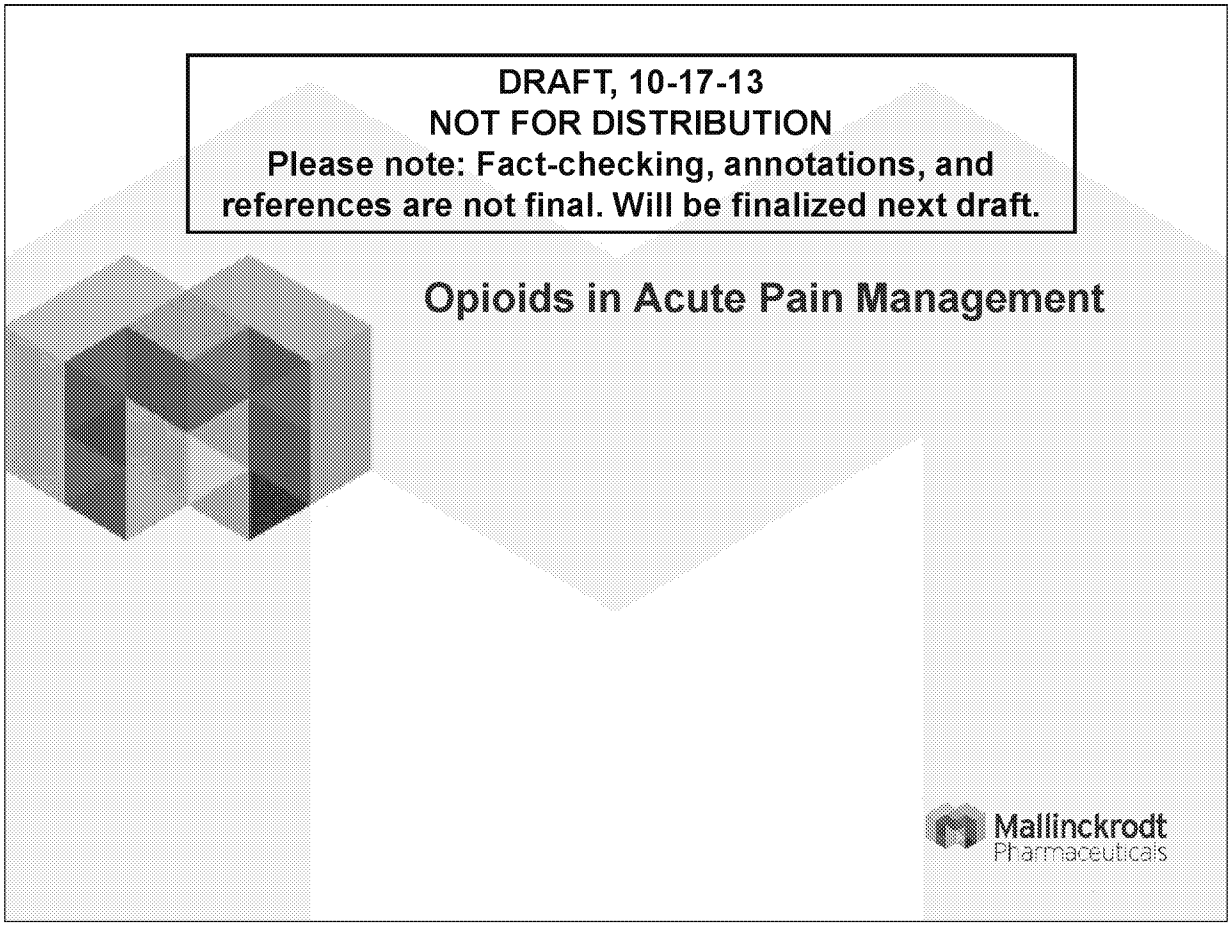
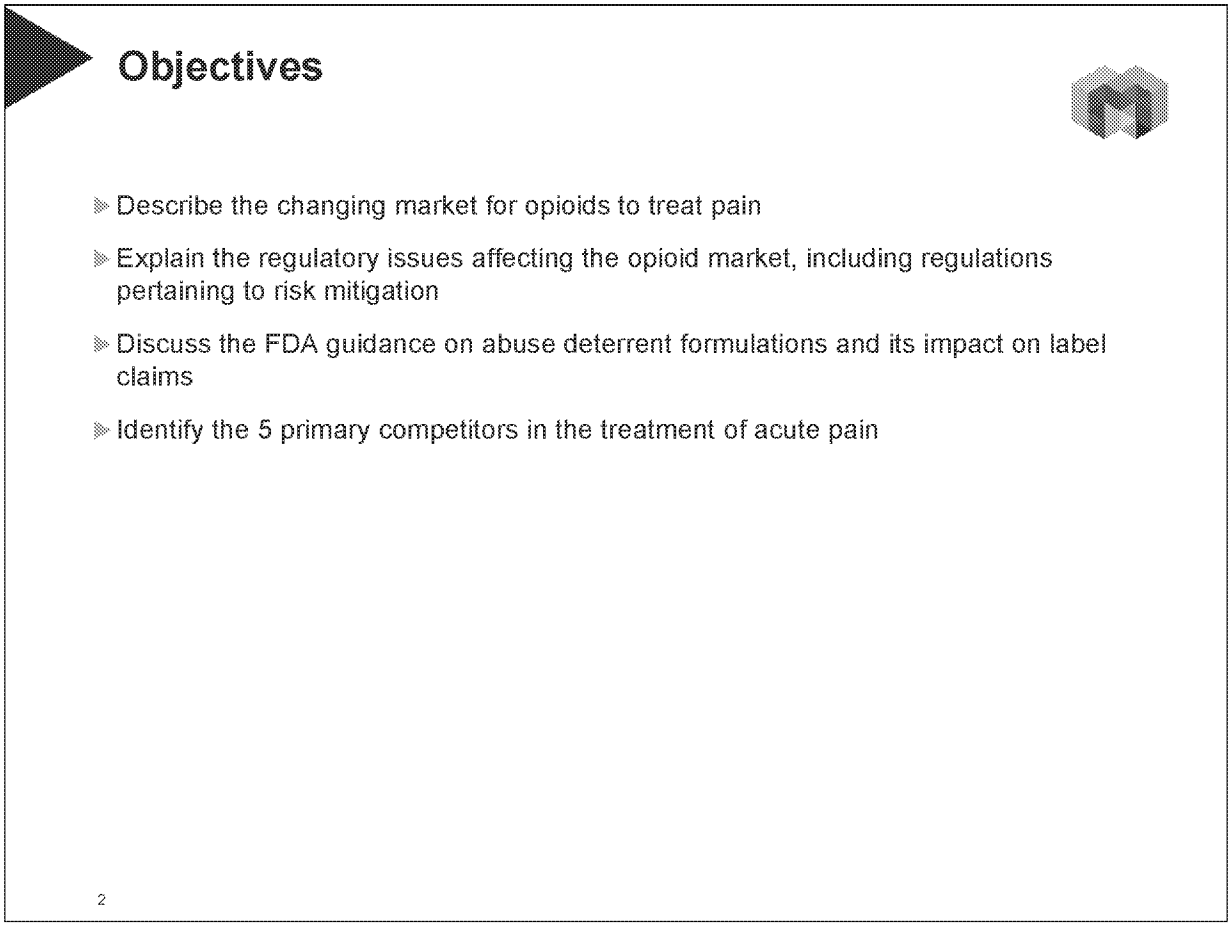
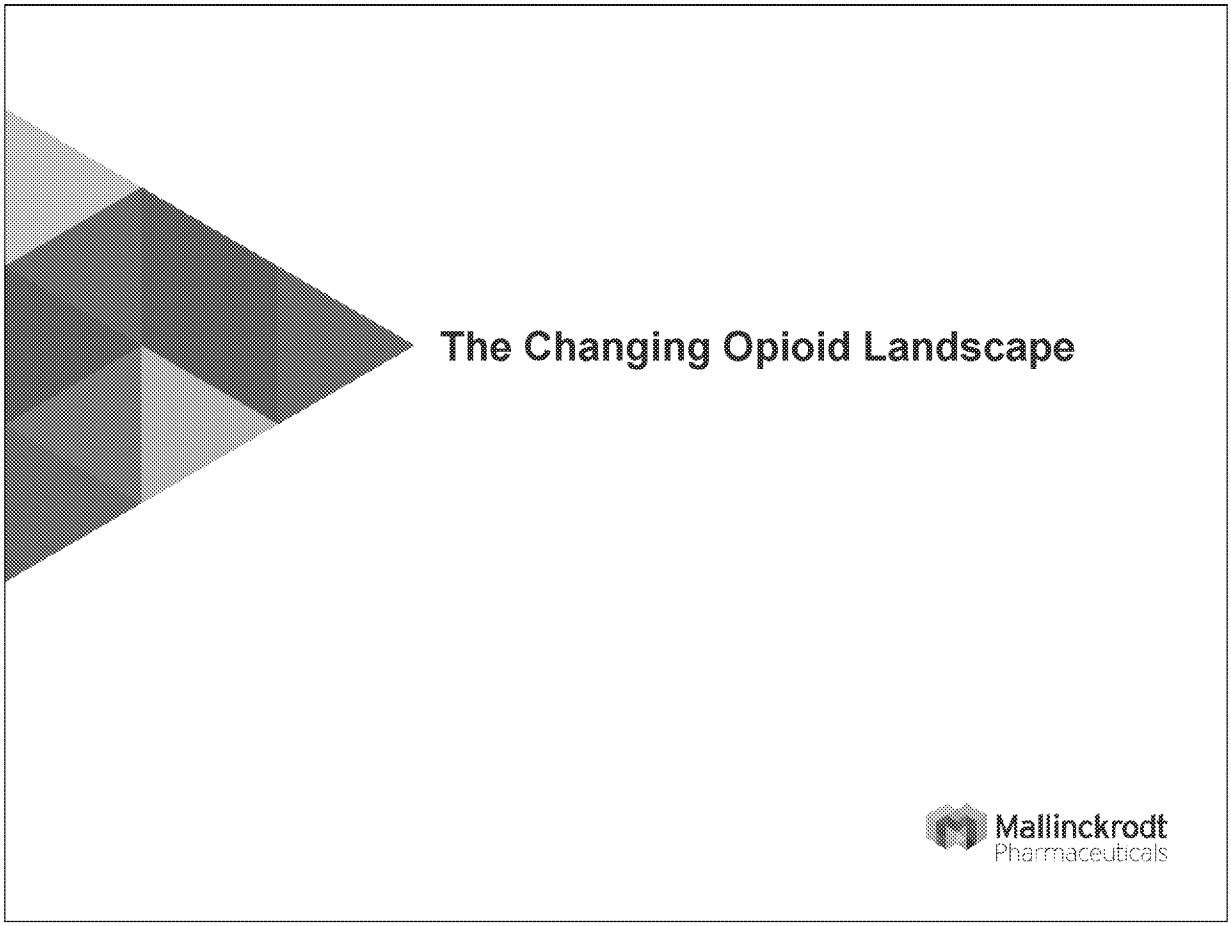
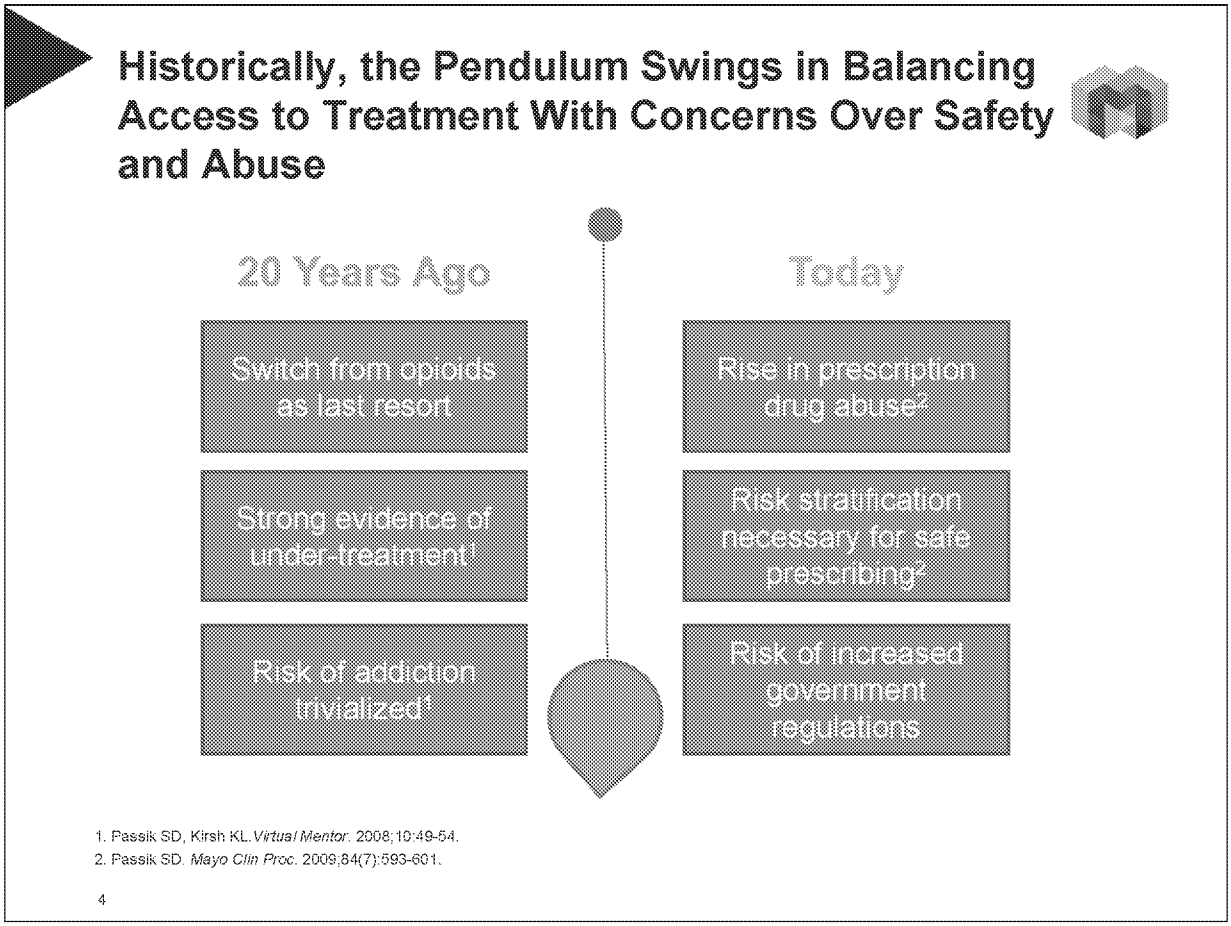
EXHIBIT 40


DRAFT, 10-17-13
NOT FOR DISTRIBUTION
Please note: Fact-checking, annotations, and references are not final. Will be finalized next draft.
Opioids in Acute Pain Management
Mallinckrodt
Pharmaceuticals



Upon completing review of this topic, the participant will be able to:
Describe the changing market for opioids to treat pain
Explain the regulatory issues affecting the opioid market, including regulations pertaining to acetaminophen and abuse deterrence
Describe current abuse deterrence products and overview concepts in the pipeline
Identify the 5 primary competitors in the treatment of acute pain


The Changing Opioid Landscape
Mallinckrodt
Pharmaceuticals



Opioids are effective in treating pain and have been available for thousands of years.1 Historically, in society issues around the use of opioids swing like a pendulum from balancing access to treatment for patients with pain to increased concerns over safety and abuse. At one extreme, irrational fear of addiction resulted in substantial under-treatment of pain.1 Two decades ago, the prevailing view shifted to the other extreme of trivializing the risk for addiction.1 Successful treatment of cancer patients without incurring addiction led to a belief that refraining from treating pain was unethical. Indiscriminate use of opioids resulted in greater availability of prescription pain medications as well as in a rise in their abuse.2 In turn, this has led to a more balanced understanding that risk stratification is important for safe prescribing and that government regulation is needed to moderate the public health consequences of abuse of prescription pain medications.1,2

References

Passik SD, Kirsh KL. Double standard for pain management. Virtual Mentor. 2008;10:49-54.
Passik SD. Issues in long-term opioid therapy: umnet needs, risks, and solutions. Mayo Clin Proc. 2009;84(7):593-601.

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Passik SD, Kirsh KL. Double standard for pain management. Virtual Mentor. 2008;10:49-54.
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American Academy of Pain Medicine. http://www.painmed.org/advocacy/rems/opioid-risk-evaluation-and-mitigation-strategies-rems-update/ Accessed September 6, 2013.

Passick, 2008 pg 49 (A)
Passick, 2008 pg 49 (B)

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Passick, 2008 pg 49 (A)
Passick, 2008 pg 49 (C)
Passick, 2008 pg 49 (B)
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Passick, 2009 pg 596 (A)
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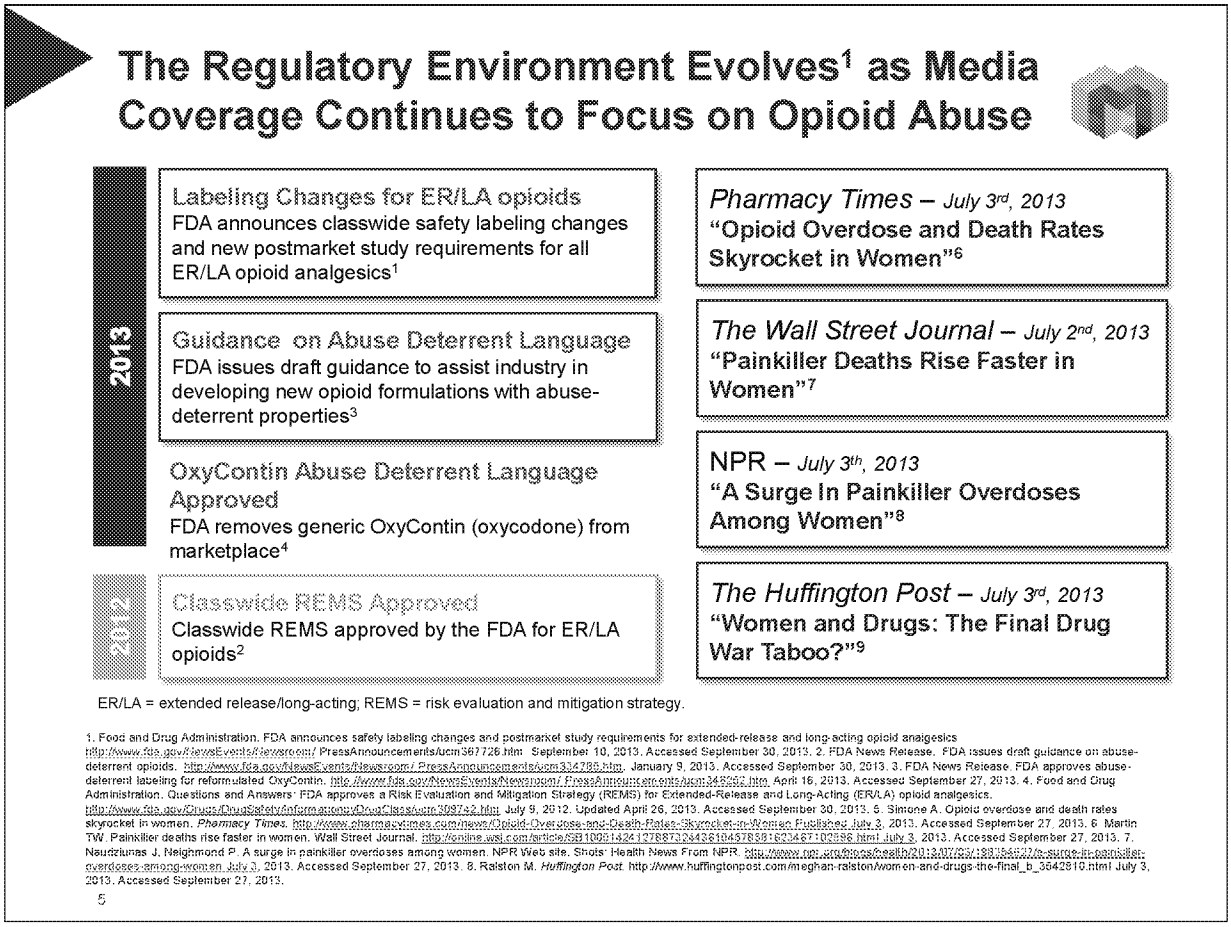
Passick, 2008pg 50 (A)
AAPM, 2013 p.1 A



The regulatory environment is currently evolving in an attempt to balance challenges of access to treatment with concerns over safety and abuse.1 In 2012, classwide risk evaluation and mitigation strategies (REMS) were approved by the FDA, which include voluntary training for prescribers on opioids.2 In January 2013, the FDA issued guidance for manufacturers on abuse-deterrent opioids.3 The guidance was specific to study design, study evaluation and label claims resulting from these studies. Also in 2013, the FDA approved language confirming abuse-deterrent properties of OxyContin and removes generic OxyContin (oxycodone) from the marketplace.4 In September 2013, the FDA announced safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics.5

As the regulatory environment evolves, opioid abuse continues to be a focus in the media. Opioid pain medications have been in the news for many years, but here we show some of the key headlines since the release of the July 2013 CDC Report. The report focused on the rise of abuse and abuse-related outcomes for women, but the story is the same across other populations, including the Medicare population and teens between 12-17 years of age. These headlines clearly illustrate the degree of interest in this issue as well as the media focus on opioid abuse and its ramifications as a high-profile, national issue.6-9

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FDA News Release. FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics http://www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm367726.htm Accessed September 11, 2013.
Simone A. Opioid Overdose and Death Rates Skyrocket in Women. Pharmacy Times. July 3, 2013.
Martin TW. Painkiller Deaths Rise Faster in Women. Wall Street Journal. July 2, 2013.
Naudziunas J et al. A Surge in Painkiller Overdoses Among Women. NPR. July 3, 2013.
Ralston M. Women and Drugs: The Final Drug War Taboo? Huff Post. July 3, 2013.

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FDA News Release Sep 2013
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Ref 8 page 1
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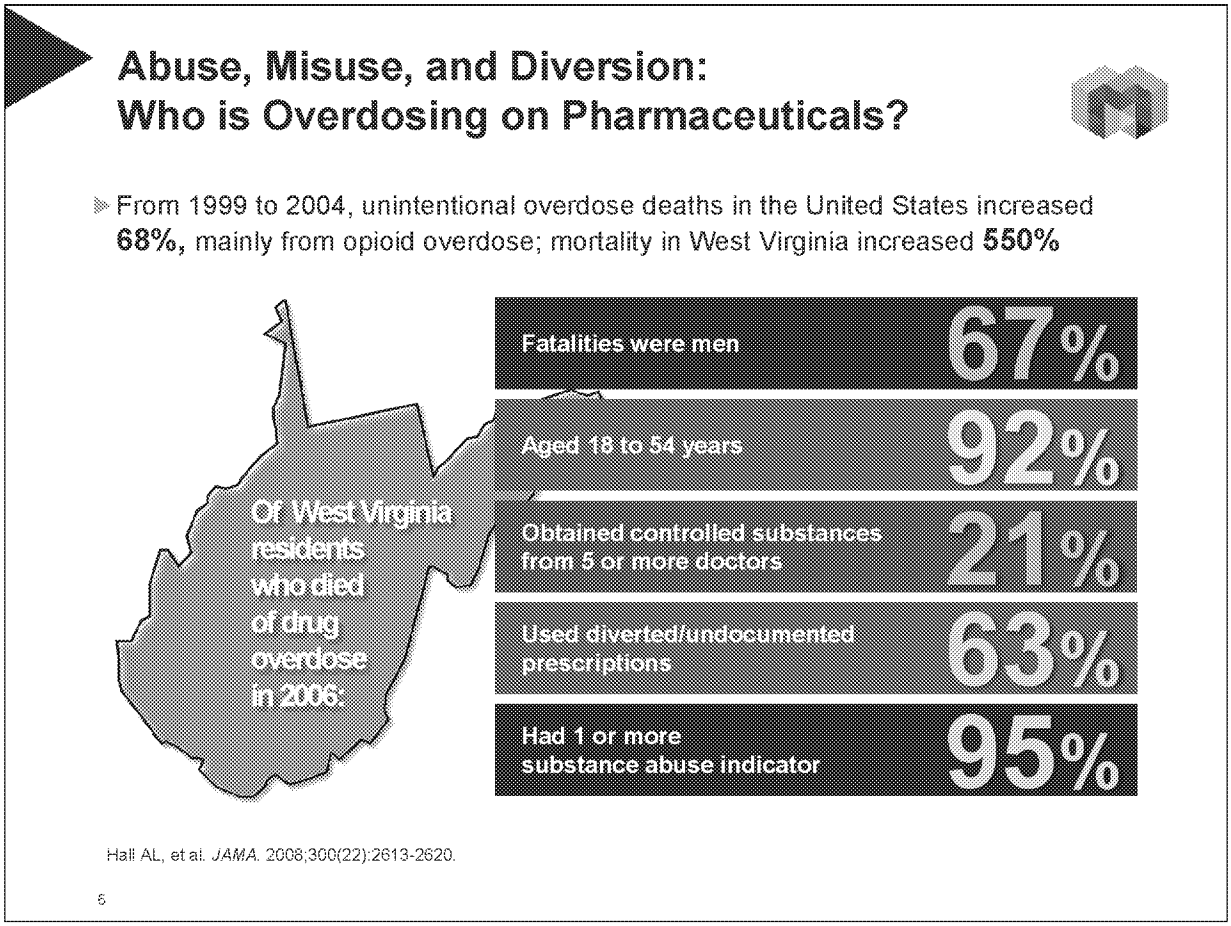
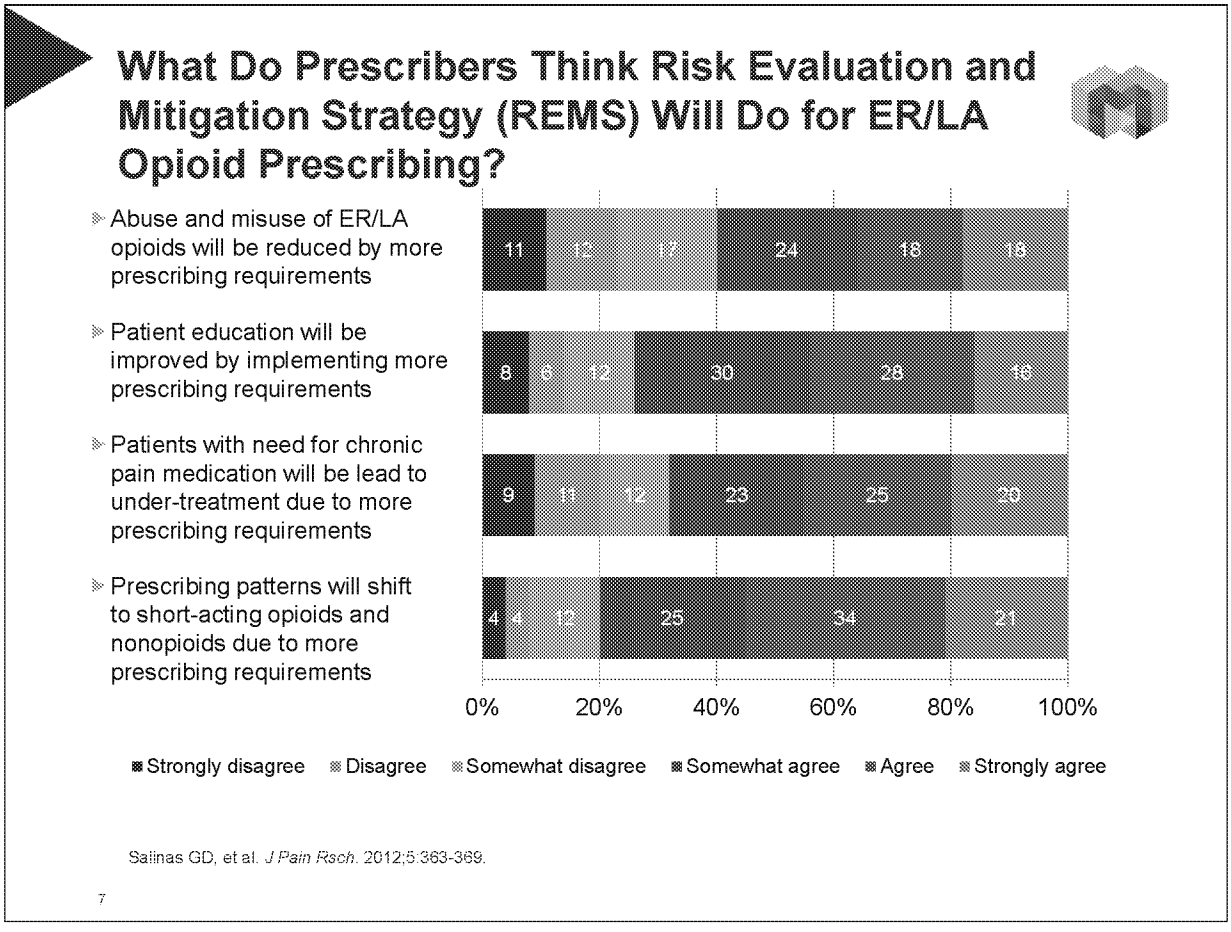


Epidemiologically, in the United States the effects of what has been called a pharmacoepidemic have been most pronounced in the rural states, such as West Virginia, where the nation's largest overdose mortality increase occurred from 1999 through 2004. This study evaluated the risk factors most associated with those who died of unintentional pharmaceutical overdose in West Virginia in 2006. Nearly all of the unintentional overdose deaths involved prescription drugs and prescription opioids played a significant role in these deaths. Fewer than 25% of these deaths involved alcohol, illicit drugs or routes of administration considered nonmedical. Of all 295 persons who died, multiple substances contributed to the fatal overdose in 234 (79.3%) of these individuals. With a range of 1 to 5, the mean number of contributing prescription drugs was 2. Opioids were the most prevalent drug class, contributing to 93.2% of the fatalities, 44.4% of which were associated with prescription documentation for all contributing opioids. Methadone was the most commonly identified drug and was involved in 112 (40.0%) of the deaths.

Prescribing clinicians are urged to follow guidelines and to refer patients to pain management specialists as needed. They are also urged to consult state drug monitoring programs, available in most states, in order to see if their patients are securing scheduled drugs from other doctors.

References

1. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300(22):2613-2620.



What do prescribers think about increased regulatory efforts to reduce abuse and increase safety in the use of opioids? Primary care physicians were asked to evaluate how they felt about the 4 bulleted statements regarding the effect of REMS on opioid prescribing and to rate whether they disagreed or agreed on a scale (strongly disagree, disagree, somewhat disagree, somewhat agree, agree and strongly agree). A significant number of these PCPs are cautious about the additional requirements that REMS policies may place on them and how these policies may impact their patients, as reflected above. Only about 8 of them consider themselves very familiar with the FDA REMS requirements, and many PCPs who responded to this survey felt that increased requirements will have a negative impact on pain management without positively impacting patient education and drug abuse or misuse. More than 50% felt that including a medication guide in the requirements would have no impact on patient care, and 24% felt the same regarding communication plans.1

References

1. Salinas GD, Robinson CO, Abdolrasulnia M. Primary care physician attitudes and perceptions of the impact of FDA-proposed REMS policy on prescription of extended-release and long-acting opioids J Pain Rsch. 2012;5:363-369.

Overall, the Pain Treatment Market Grows Despite Increased Regulation and Scrutiny in the Media

- Fifth largest drug class for pharmacy spending in 2012[1]
  - $18.2 billion on pain medications[1]
- In 2011, $8.3 billion was spent on opioids alone, an increase of 123% since 2007[2]

1 IMS Institute for Healthcare Informatics. Declining medicine use and costs: For better or worse. Parsippany NJ; May 2013. Available at: static.correofarmaceutico.com/docs/**2013**/05/20/usareport.pd

2. Manchikanti L, Helm S 2nd, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15(3 Suppl):ES9-ES38.

8

The pain treatment market continues to grow despite legal and regulatory changes and media coverage that address increasing morbidity and mortality associated with nonmedical use of prescription pain medications.1 In 2012, $18.2 billion was spent on pain medications in the United States, making it the fifth largest drug class for pharmacy expenditures.2 In 2011, $8.34 billion was spent on opioids, an increase of 123% since 2007.3

References

American Academy of Pain Medicine. Opioids Risk Evaluation and Mitigation Strategy (REMS) Update April 2011. http://www.painmed.org/advocacy/rems/opioid-risk-evaluation-and-mitigation-strategies-rems-update/ Accessed September 30, 2013.

IMS Institute for Healthcare Informatics. Declining medicine use and costs: For better or worse. Parsippany NJ; May 2013. Available at: static.correofarmaceutico.com/docs/2013/05/20/usareport.pd

Manchikanti L, Helm S 2nd, Fellows B, et al. Opioid epidemic in the United States. Pain Physician. 2012;15(3 Suppl):ES9-ES38.

Example image:
http://davidsollars.com/wp-content/uploads/2012/12/Neck-Pain1.jpg

IMS 2013 pg 2 (A)

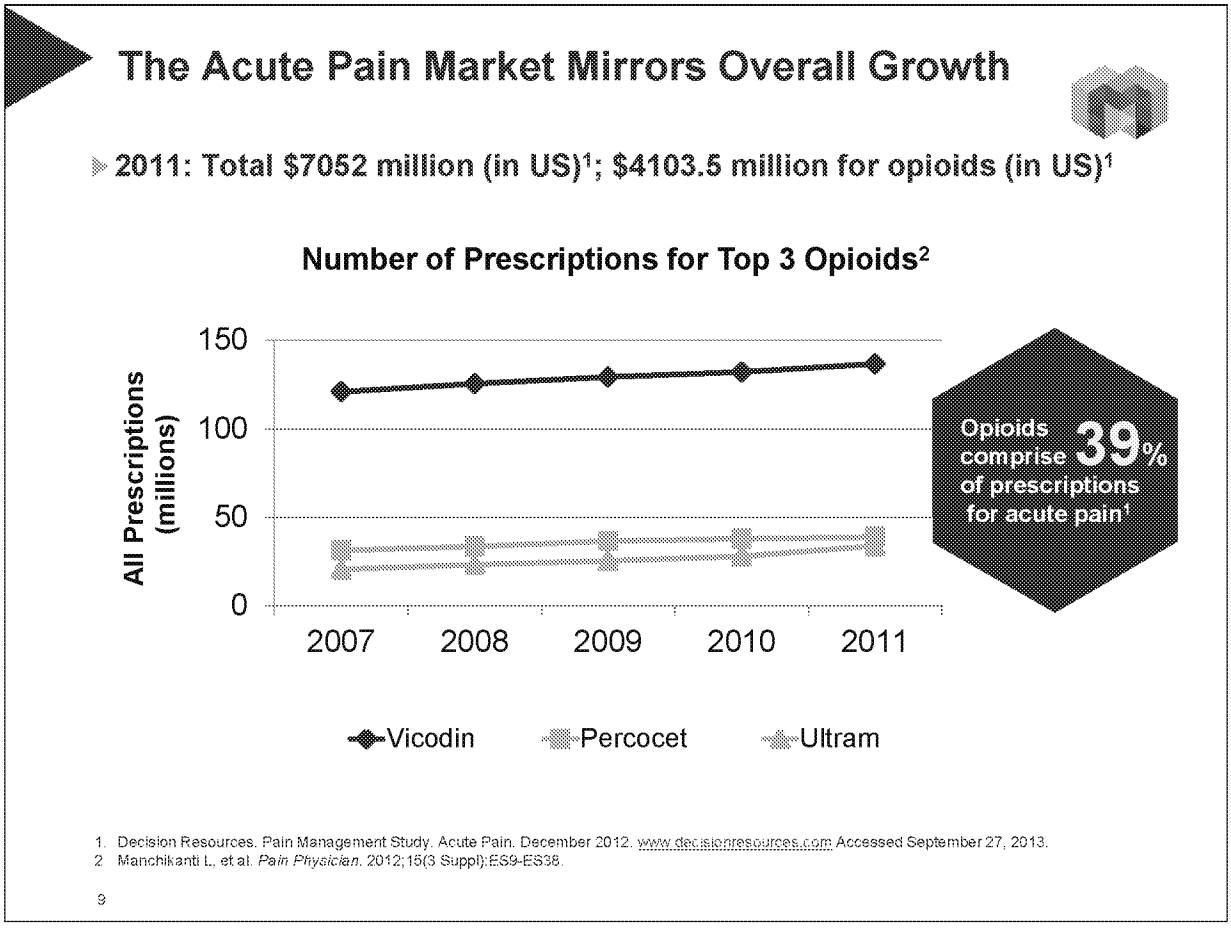
IMS 2013 pg 32 (A)

American Academy of Pain Medicine. http://www.painmed.org/advocacy/rems/opioid-risk-evaluation-and-mitigation-strategies-rems-update/ Accessed September 6, 2013.

IMS Institute for Healthcare Informatics. Declining medicine use and costs: For better or worse. Parsippany NJ; May 2013.

Manchikanti L, et al. Opioid Epidemic in the United States. Pain Physician 2012; 15:ES9-ES38.

Manchikanti, 2012 p. ES26 Table 7
IMS 2013 pg 2 (A)
IMS 2013 pg 32 (A)
Manchikanti, 2012 p. ES26 Table 7
AAPM, 2013 p.1 A



Of all prescriptions for acute pain, 39% are for opioids, accounting for $4103.5 million in sales in the US in 2011. Between 2007 and 2011, the opioid market remained stable. By far the largest number of prescriptions have been written for Vicodin® (acetaminophen and hydrocodone). Percocet® (oxycodone and acetaminophen) and Ultram® (tramadol hydrochloride) are a distant second and third, respectively.

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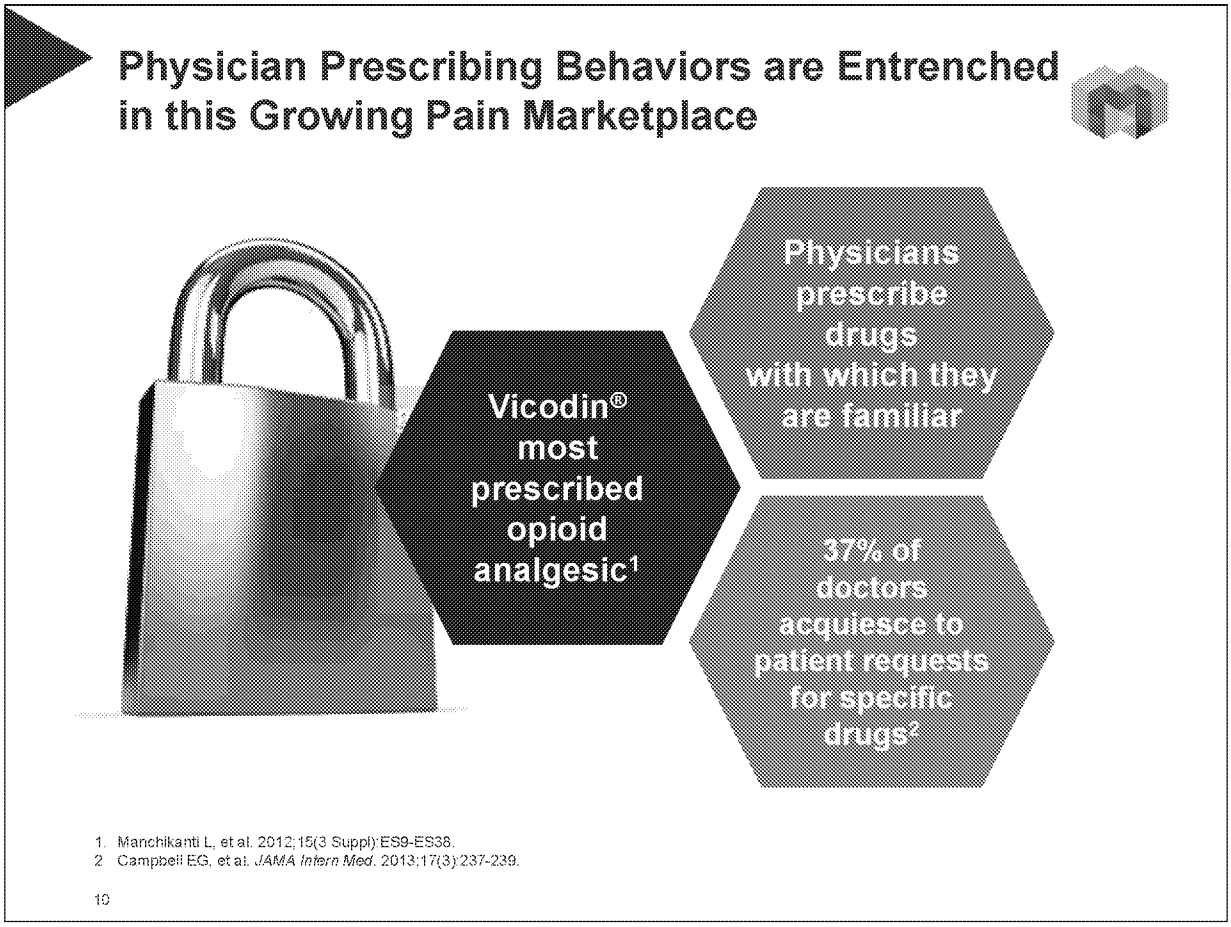
Manchikanti L, Helm S 2nd, Fellows B, et al. Opioid epidemic in the United States. Pain Physician. 2012;15(3 Suppl):ES9-ES38.

Decision Resources p 163A

Decision Resources p 2A

Manchikanti p ES23A

Manchikanti p ES25A



Market share for Vicodin, Percocet, and Ultram have remained stable since at least 2007. This is attributable, in part, to entrenched physician prescribing habits in this growing marketplace. Physicians have a tendency to prescribe their patients drugs with which they are familiar. Moreover, when patients ask for brand-name drugs, a little over one-third of physicians acquiesce despite the availability of less expensive options.

References

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Campbell EG, Pham-Kanter G, Vogeli C. Physician acquiescence to patient demands for brand-named drugs: Results of a national survey of physicians. JAMA Intern Med. 2013;17(3):237-239.

Example image:

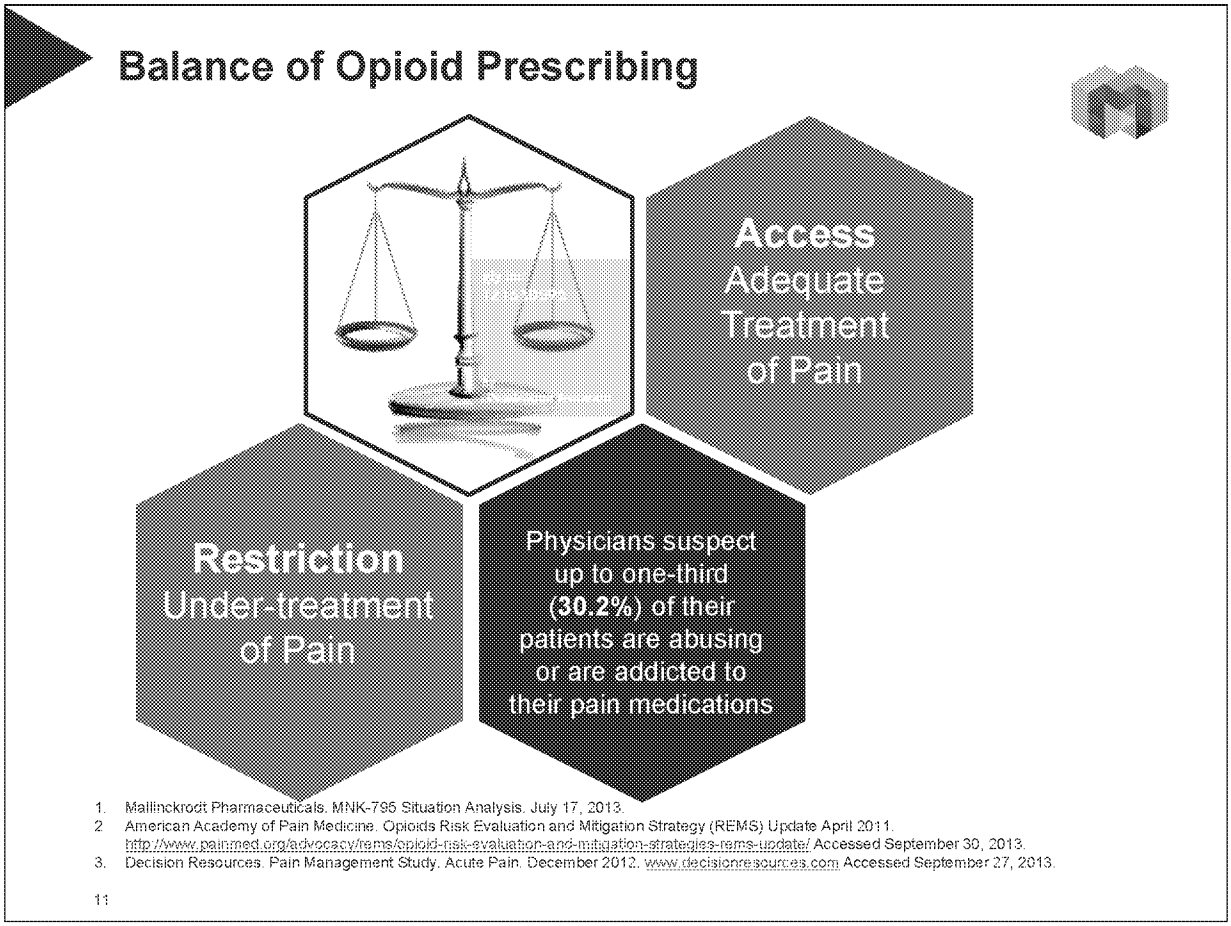
http://www.iconarchive.com/show/crystal-clear-icons-by-everaldo/Action-decrypted-icon.html

Campbell 2012 p. 237A; p238A

Manchikanti p ES25A

Campbell 2012 p. 237A; p238A

Manchikanti p ES25A



The struggle to balance adequate treatment of pain against growing opioid use and the problems of misuse continues. Mallinckrodt market research shows that physicians suspect almost one-third (30.2%) of their patients are abusing or are addicted to their pain meds.1 Pain specialists (>50%) and primary care practitioners (69%) reported that concern about diversion of opioids is a factor in prescribing.

According to Lynn Webster, MD, president-elect of the American Academy of Pain Medicine, “There are consequences for not treating pain, as there are consequences when we prescribe opioids to somebody at risk for addiction. The problem of prescription drug abuse and the problem of treating pain will require a broad coalition of people — it will require the regulatory community, medical community and legal community to jointly come together to solve this problem. No one group will be able to solve this problem by themselves.”2

This challenge provides an opportunity in the marketplace to develop abuse-deterrent formulations of opioid pain medications as well as drugs with better safety and tolerability.3

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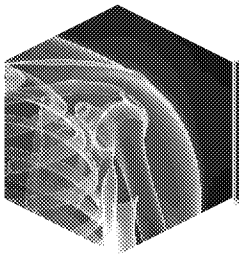
American Academy of Pain Medicine, 2012 pg 10A; pg11A

Mallinkrodt Situation Analysis slides 45

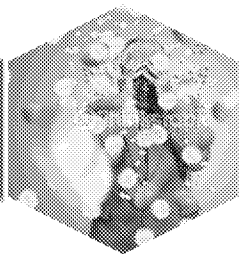
Mallinkrodt Situation Analysis slides 45, 61 and 63

Summary



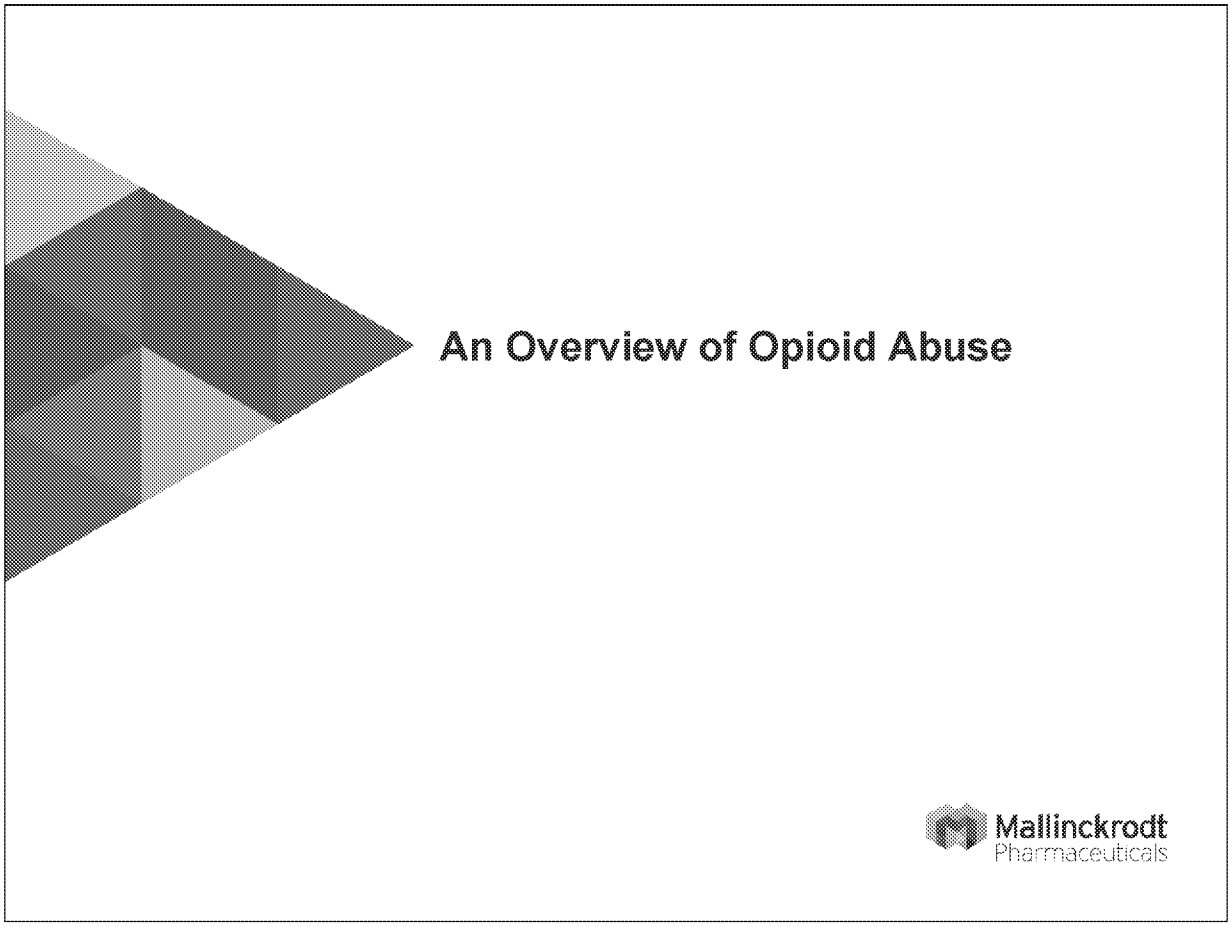
Pain is the fifth largest healthcare spending market and is still growing

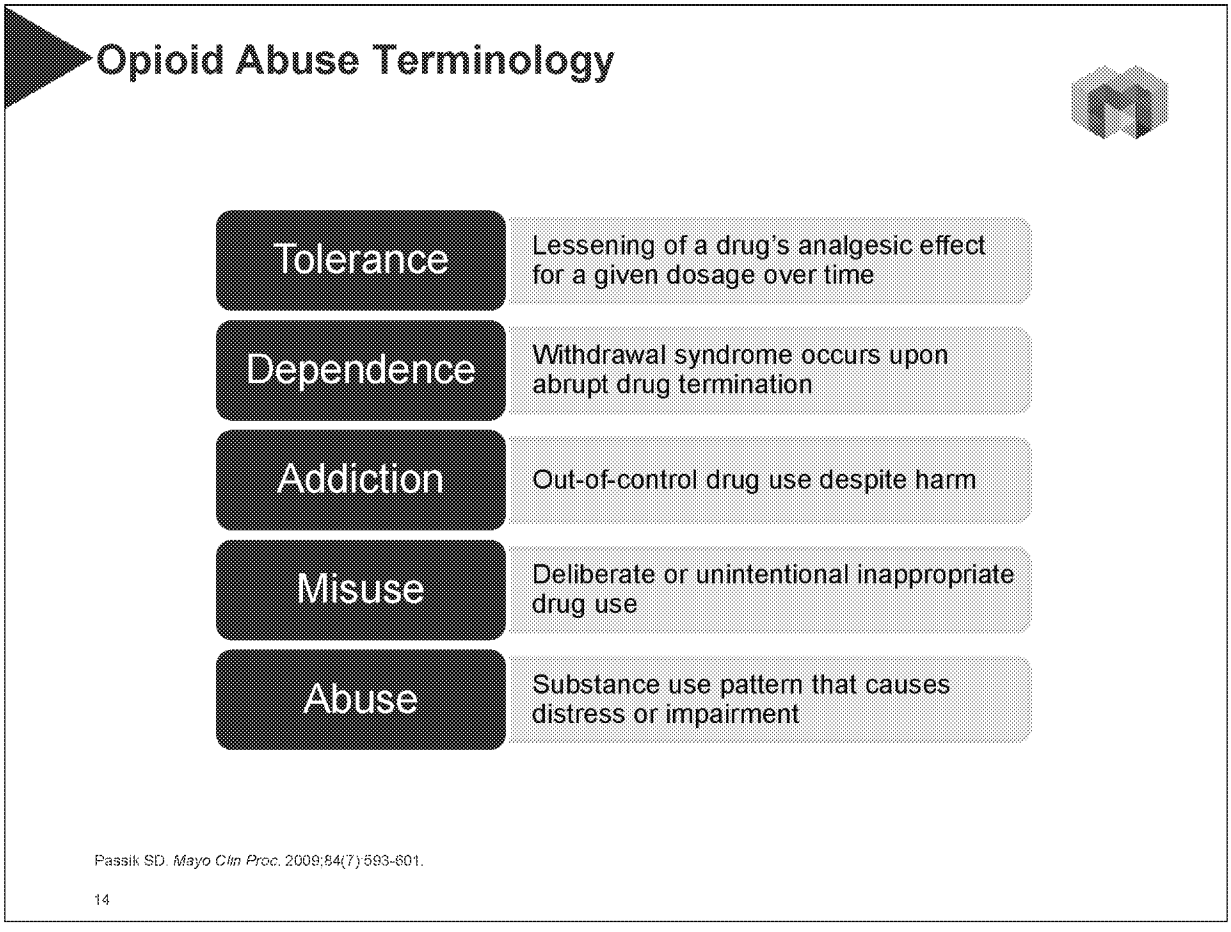
The paradigm for prescribing opioids swings from concerns about under-treatment to concerns about abuse and addiction



Acute pain is an entrenched market driven by habitual rather than intentional prescribing of Vicodin® and Percocet ®

12


An Overview of Opioid Abuse
Mallinckrodt
Pharmaceuticals



Before discussing opioid abuse we need to review terminology. Numerous terms are commonly used to describe side effects of opioid use and the problematic behaviors of addiction, misuse and abuse.

Tolerance – lessening of a drug's analgesic effect for a given dosage so a higher dose is needed to provide comparable pain relief over time
Dependence – development of withdrawal symptoms upon abrupt termination of drug treatment
Addiction – substance abuse involving out-of-control, compulsive use of drug despite harm
Misuse – not using a drug as prescribed, either deliberately or unintentionally
Abuse – maladaptive pattern of substance use leading to considerable distress or harm

References

1. Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. Mayo Clin Proc. 2009;84(7):593-601.

Example image:
http://www.hcplive.com/publications/pain-management/2011/december-2011/Abuse-deterrent-Technologies-in-Opioid-Medications-A-New-Weapon-in-the-Fight-against-Misuse-and-Abuse
Passik SD. Issues in long-term opioid therapy: Unmet needs, risks, and solutions. Mayo Clin Proc. 2009;84(7):593-601.

Passik. 2009 p. 598B.

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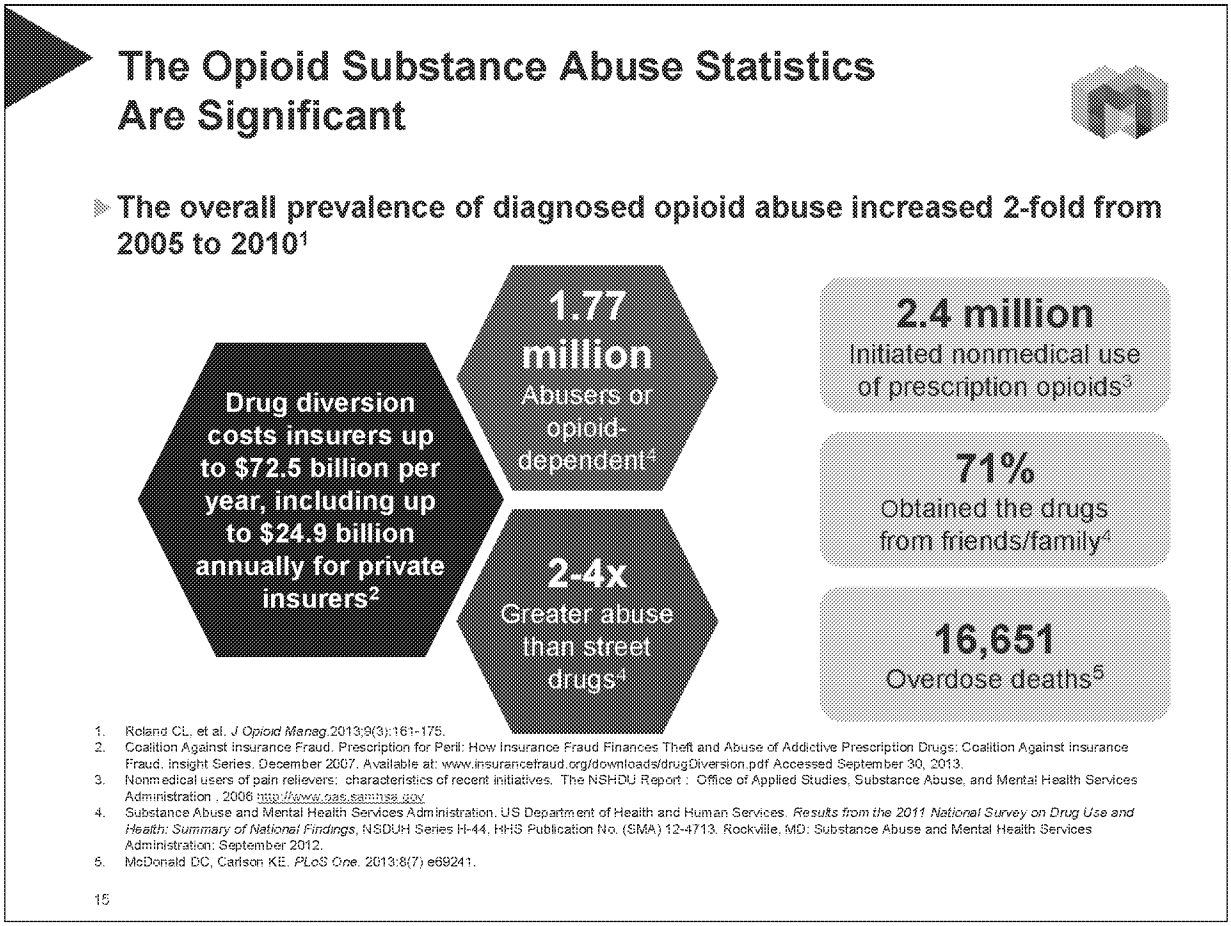

The statistics on opioid abuse are significant. In 2006, it was estimated that 2.2–2.4 million individuals initiate nonmedical use of prescription opioids in the United States each year. Nonmedical use entails use without a prescription of the individual's own, or use simply for the experience or feeling the drugs caused. There were 1.77 million abusers or drug dependent individuals in 2011; pain relievers were second only to marijuana as the products used by abusers. The percentage of users who obtained prescription drugs from friends or relatives for free was 54%, while the percentage who either purchased opioids from family or friends or took them without permission was 17% for a total of 71% obtaining drugs from family or friends. The abuse of multiple of pain relievers is 2 to 4 times that of cocaine or heroin, respectively. Use of pain relievers in abuse or drug dependence was 2.15 times greater than that of cocaine and 4.15 times greater than that of heroin. The annual costs of drug diversion for insurers are up to $72.5 billion dollars per year, with almost $25 billion in costs to private insurers. The number of overdose deaths from opioid pain relievers in 2010 was 16,651. Opioid overdose deaths are now twice as common as heroin and cocaine overdose deaths combined.

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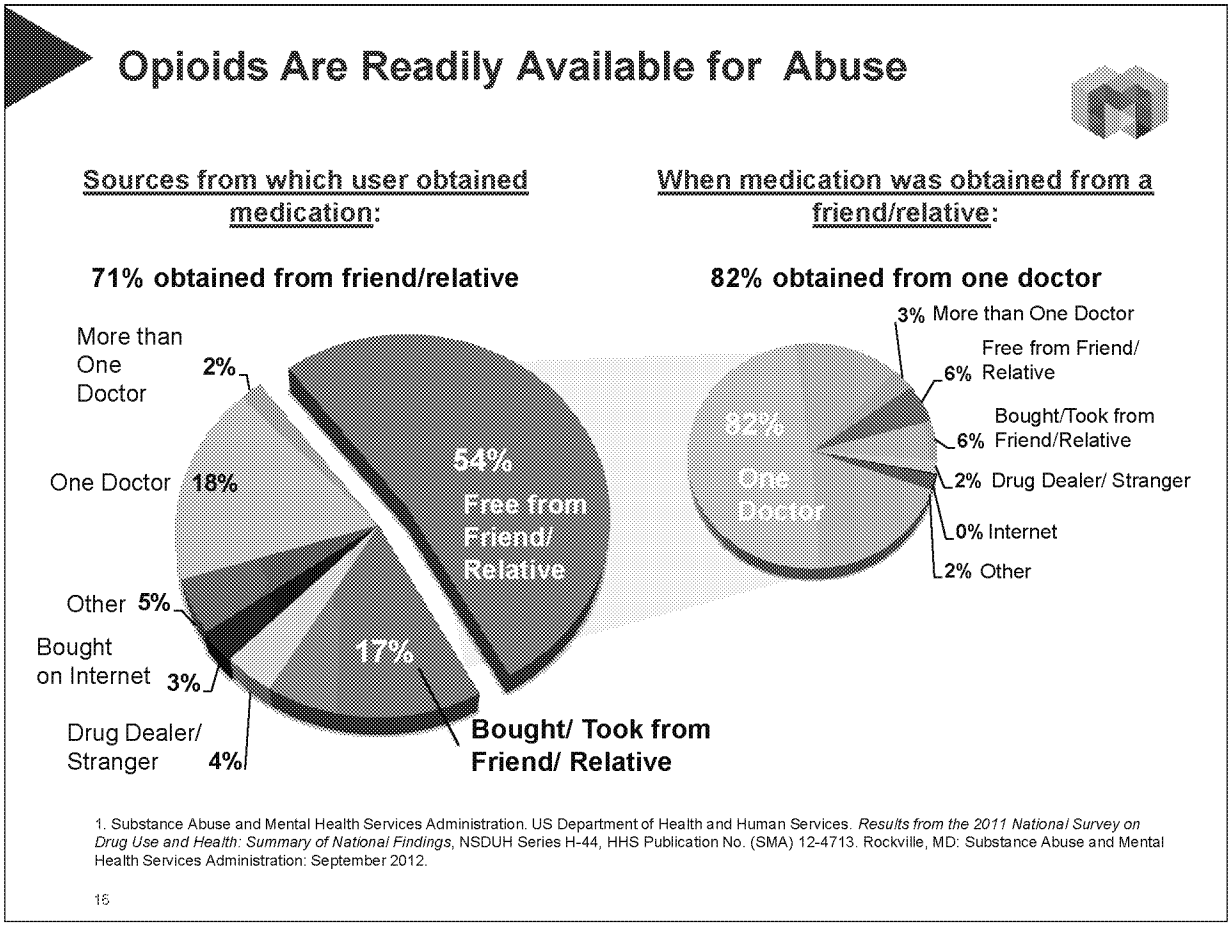

The overall message is that opioids are readily available for abuse. If we look a little deeper at the friends and relatives, of the friends or relatives, 82% obtained the drugs from a single doctor, so they were not “doctor-shopping.” The pills obtained are usually prescribed for medical use, but the prescription is not finished. The unfinished pills are then taken for nonmedical reasons by the original patient or friends/family.

References

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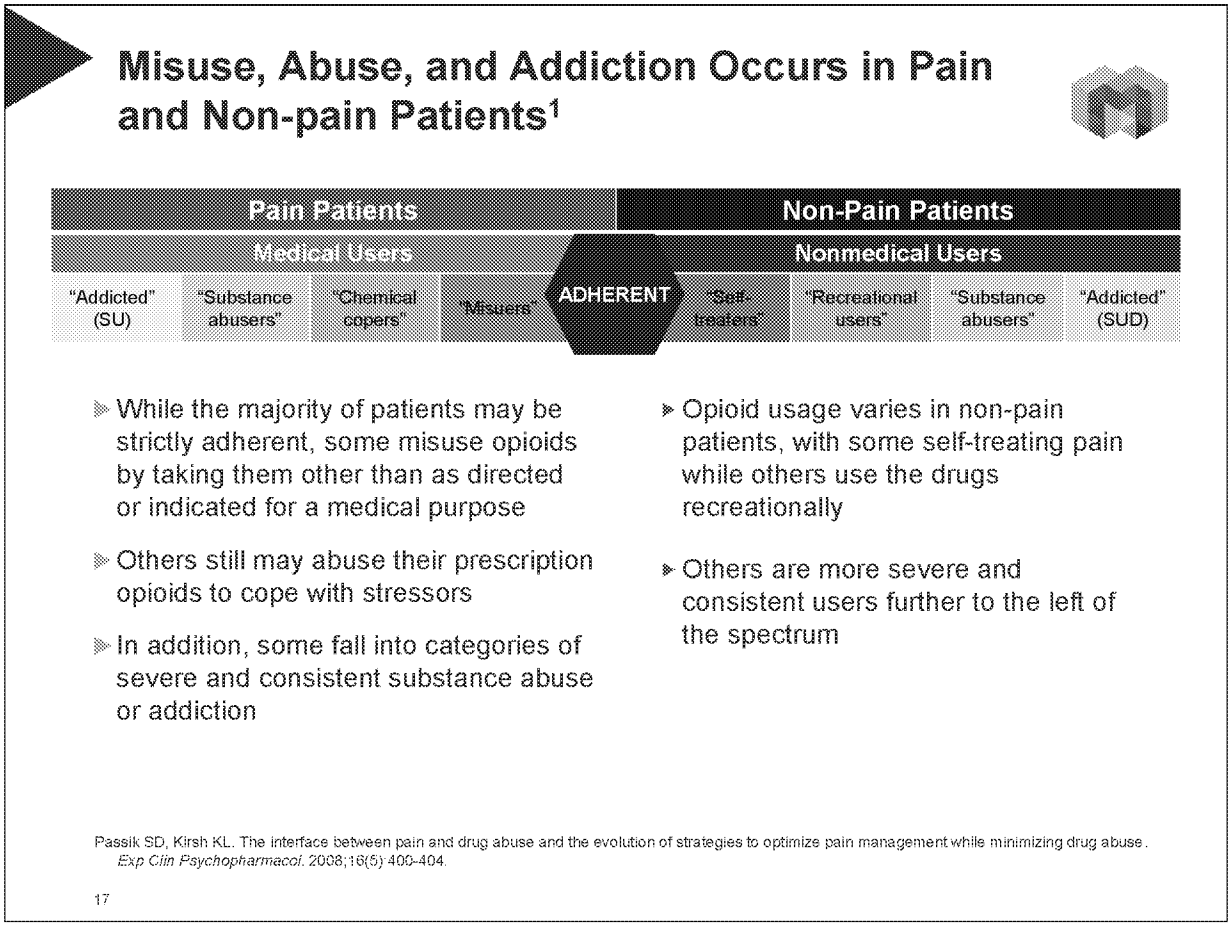
Ref 19 page 41

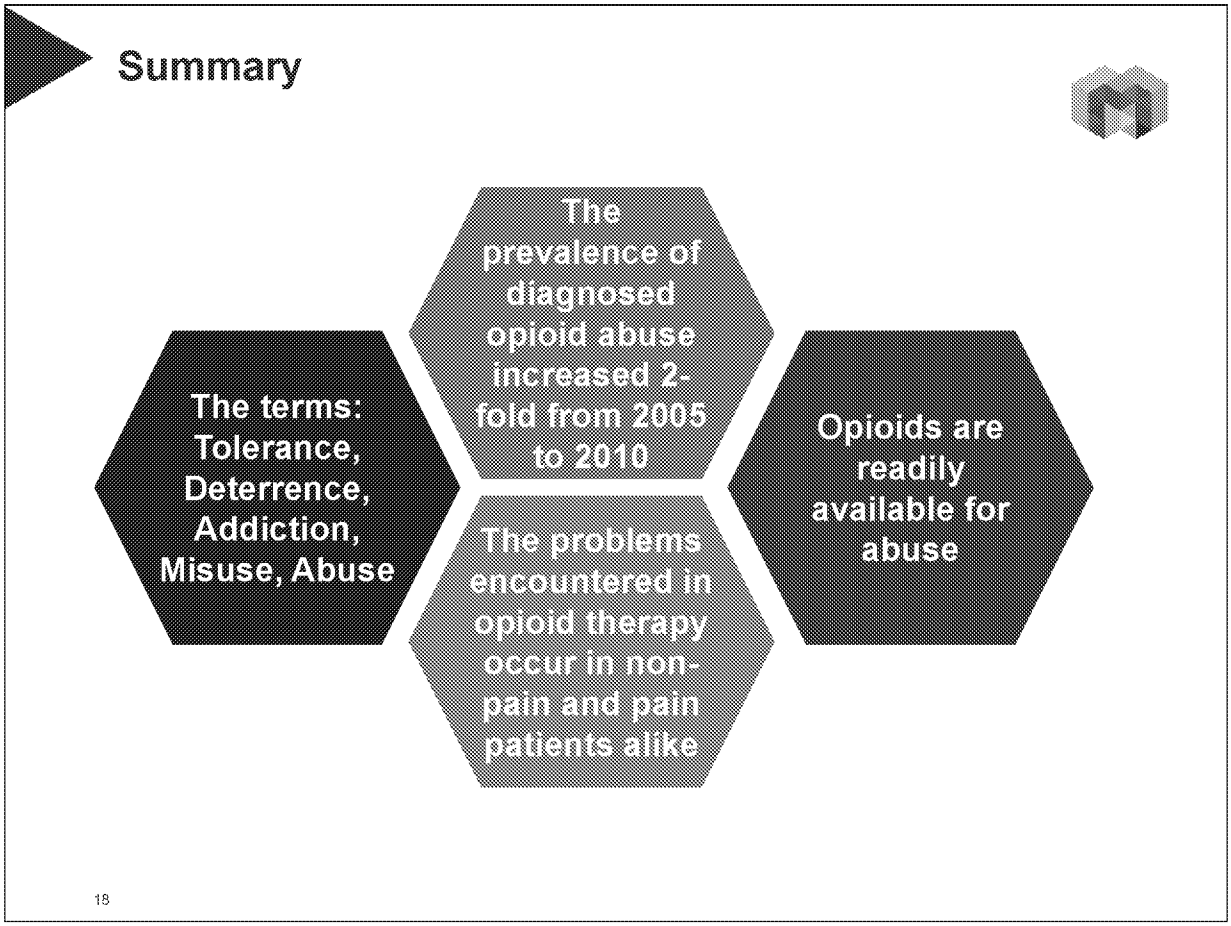


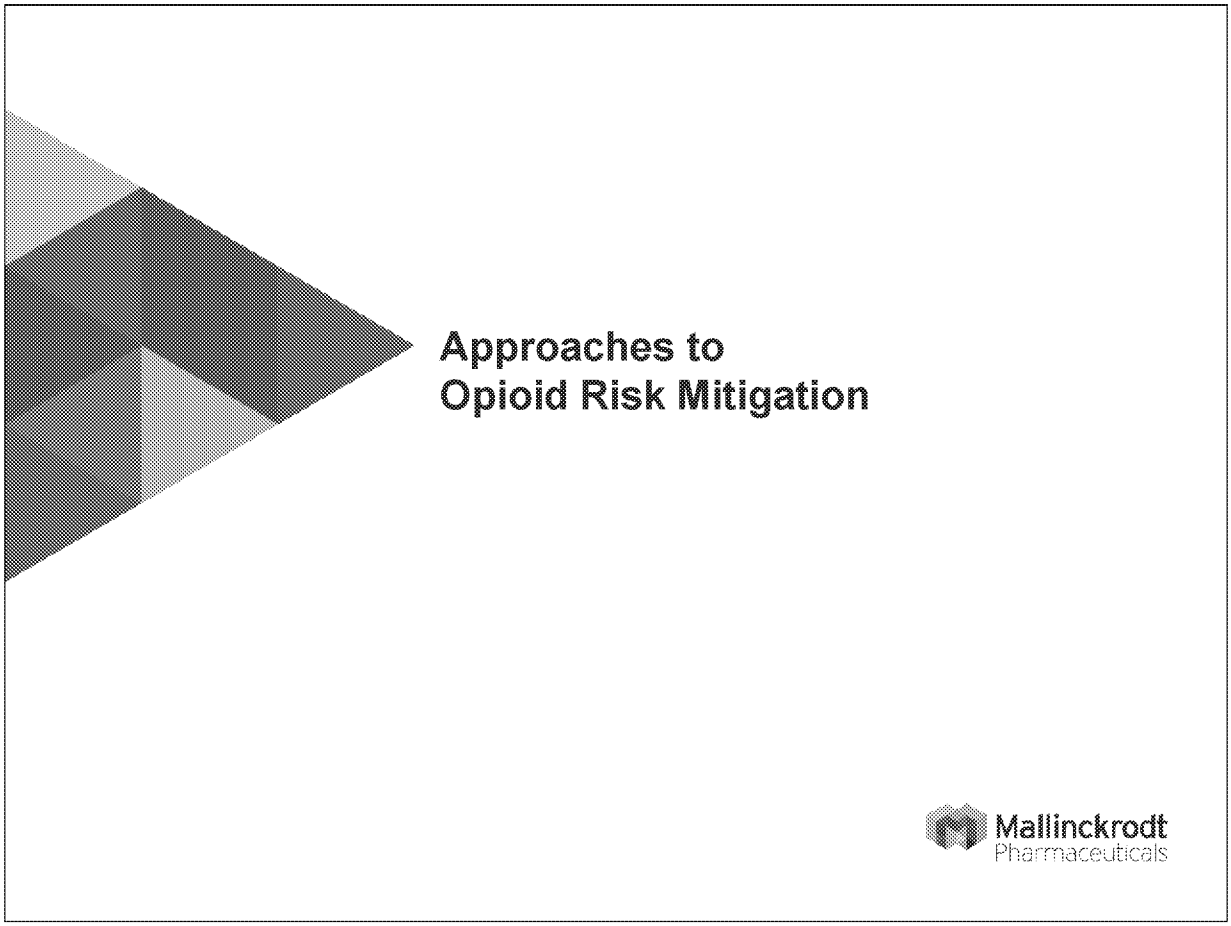
Misuse, abuse, and addiction occurs in pain and non-patients. However, the spectrum is different for pain patients vs non-pain patients. The spectrum of nonadherence in pain patients can be very complex. While the majority of patients may be strictly adherent, some misuse their prescription opioids by taking them other than as directed or indicated for a medical purpose. Still others may abuse their prescription opioids to chemically cope or may be further along the spectrum of more severe and consistent substance abuse or addiction.

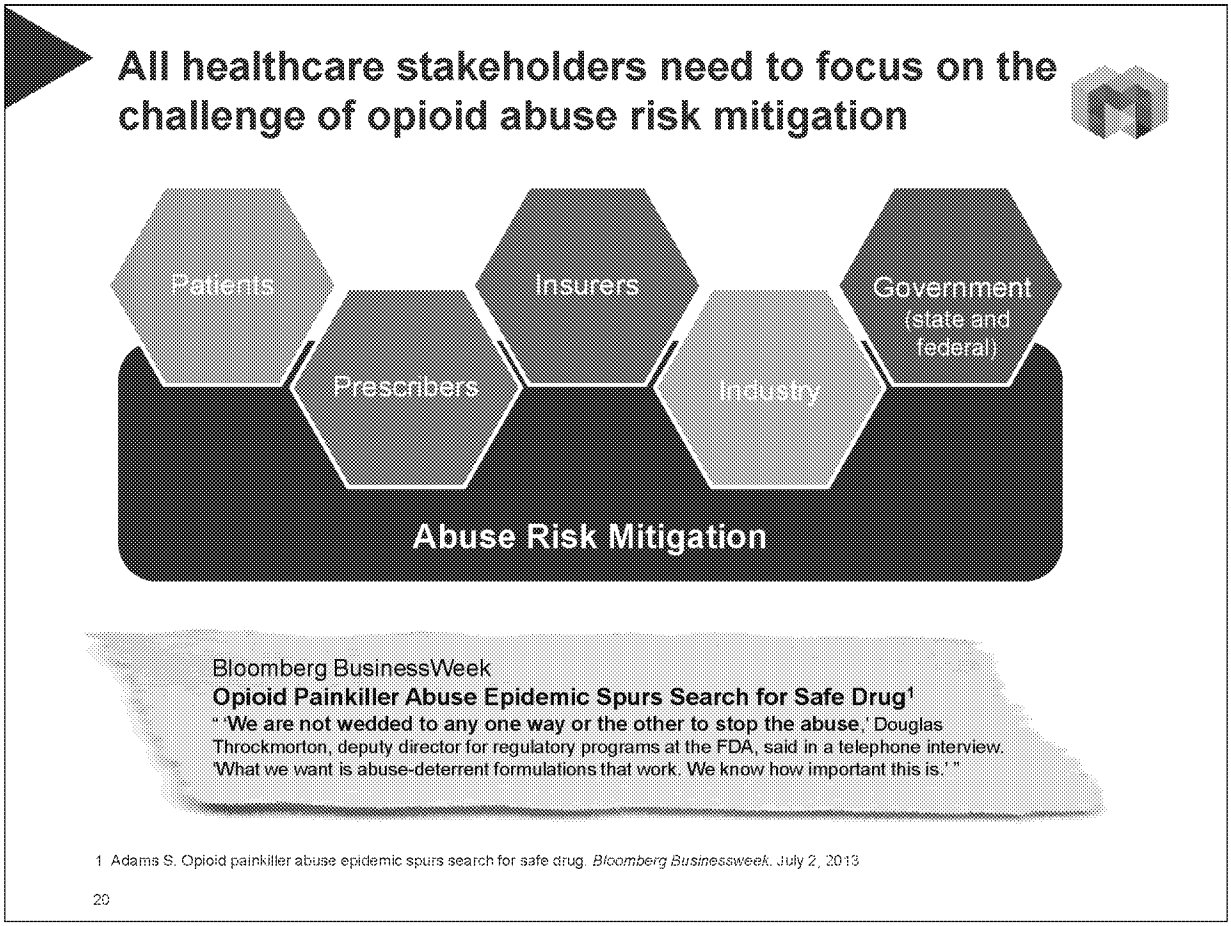
References

Passik SD, Kirsh KL. The interface between pain and drug abuse and the evolution of strategies to optimize pain management while minimizing drug abuse. Exp Clin Psychopharmacol. 2008;16(5):400-404.

Ref 1 page 2


Summary
The terms: Tolerance, Deterrence, Addiction, Misuse, Abuse
The prevalence of diagnosed opioid abuse increased 2-fold from 2005 to 2010
The problems encountered in opioid therapy occur in non-pain and pain patients alike
Opioids are readily available for abuse
18


Approaches to
Opioid Risk Mitigation
Mallinckrodt
Pharmaceuticals



All stakeholders need to be involved to tackle the challenge of opioid abuse risk mitigation; from patients on up to the government. This is everyone's problem, like Throckmorton said. We need everyone to be involved to solve the problem.

References

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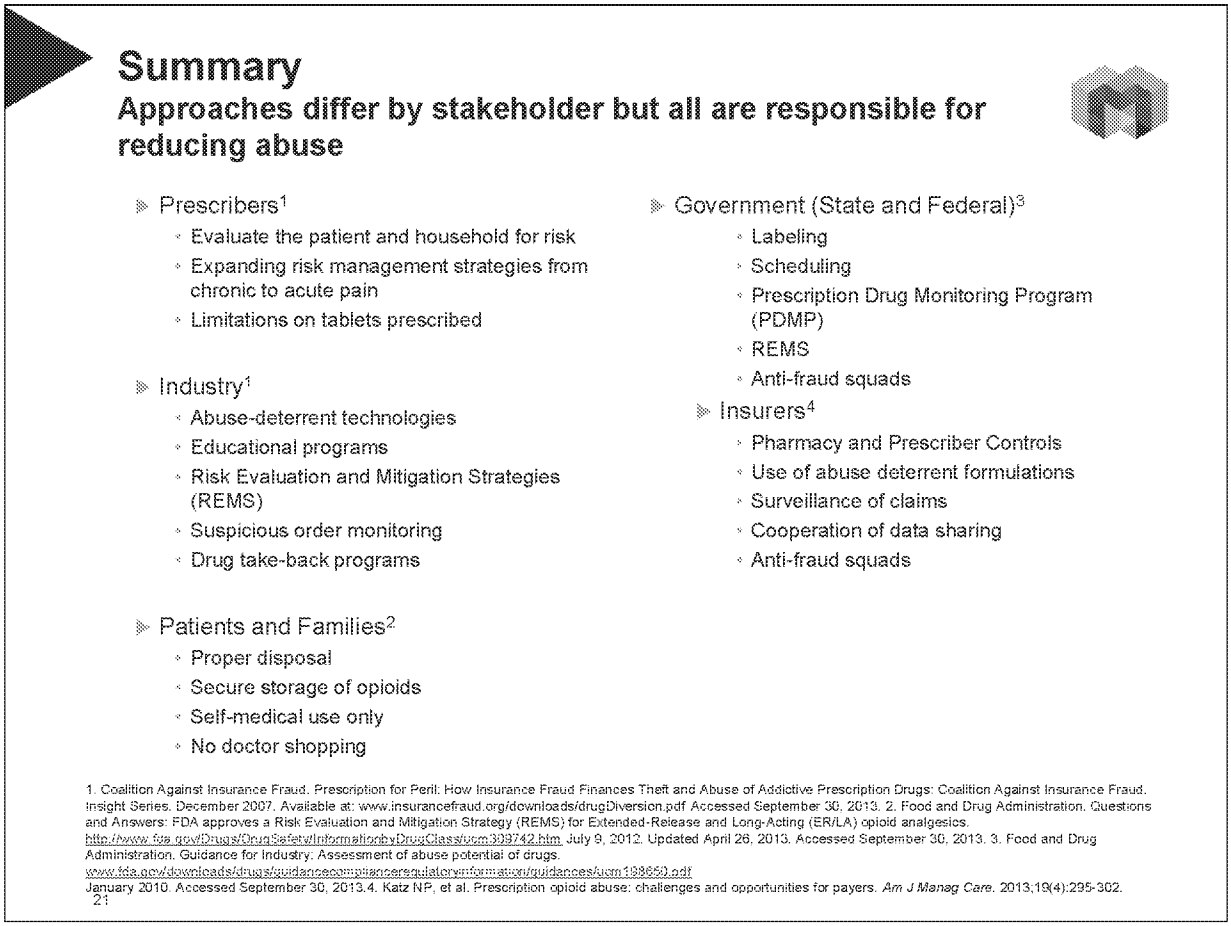
Ref 41page 1



Given the scope of the opioid abuse problem, each stakeholder group has its own set of responsibilities. Approaches differ but all are interrelated and require cooperation among all stakeholders to successfully mitigate abuse risk.

References

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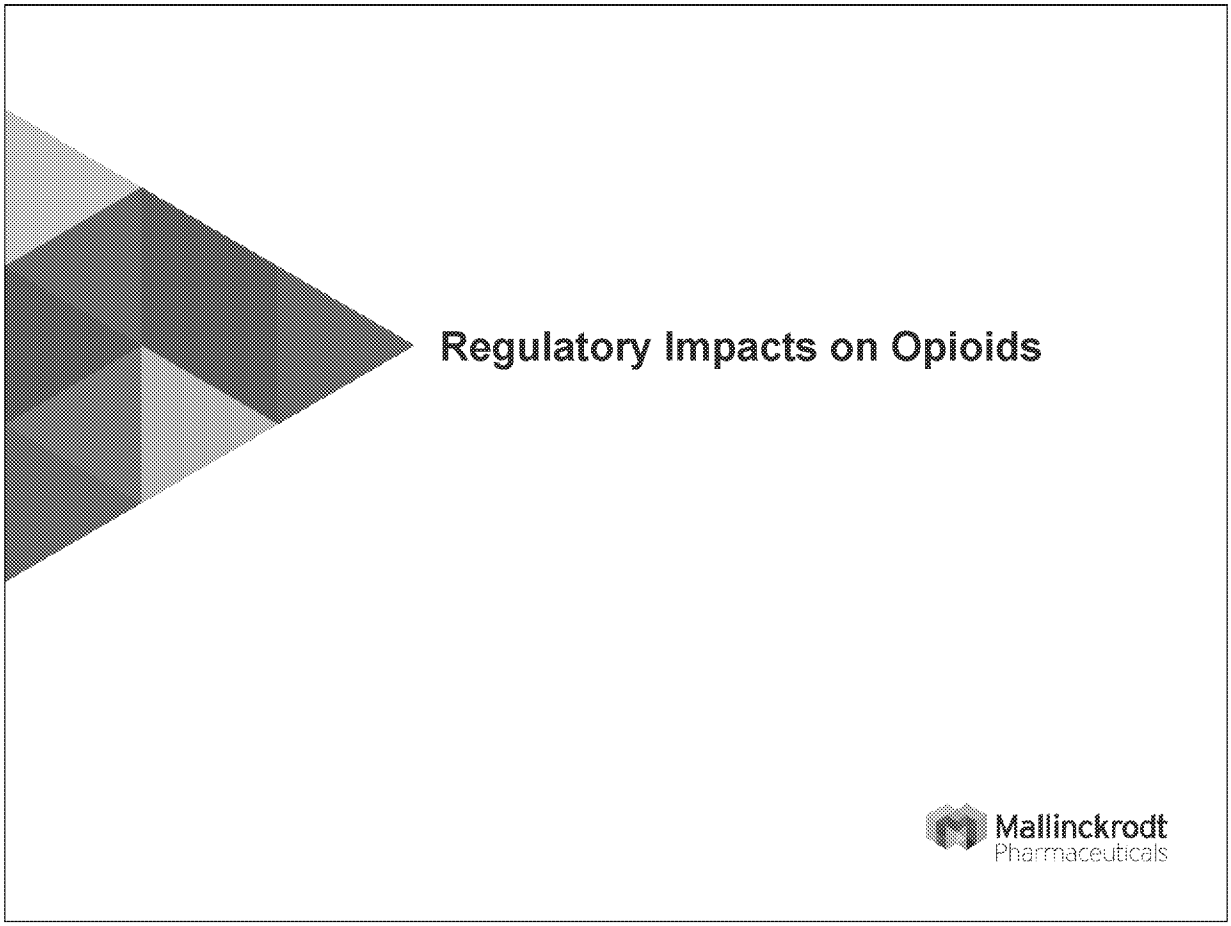
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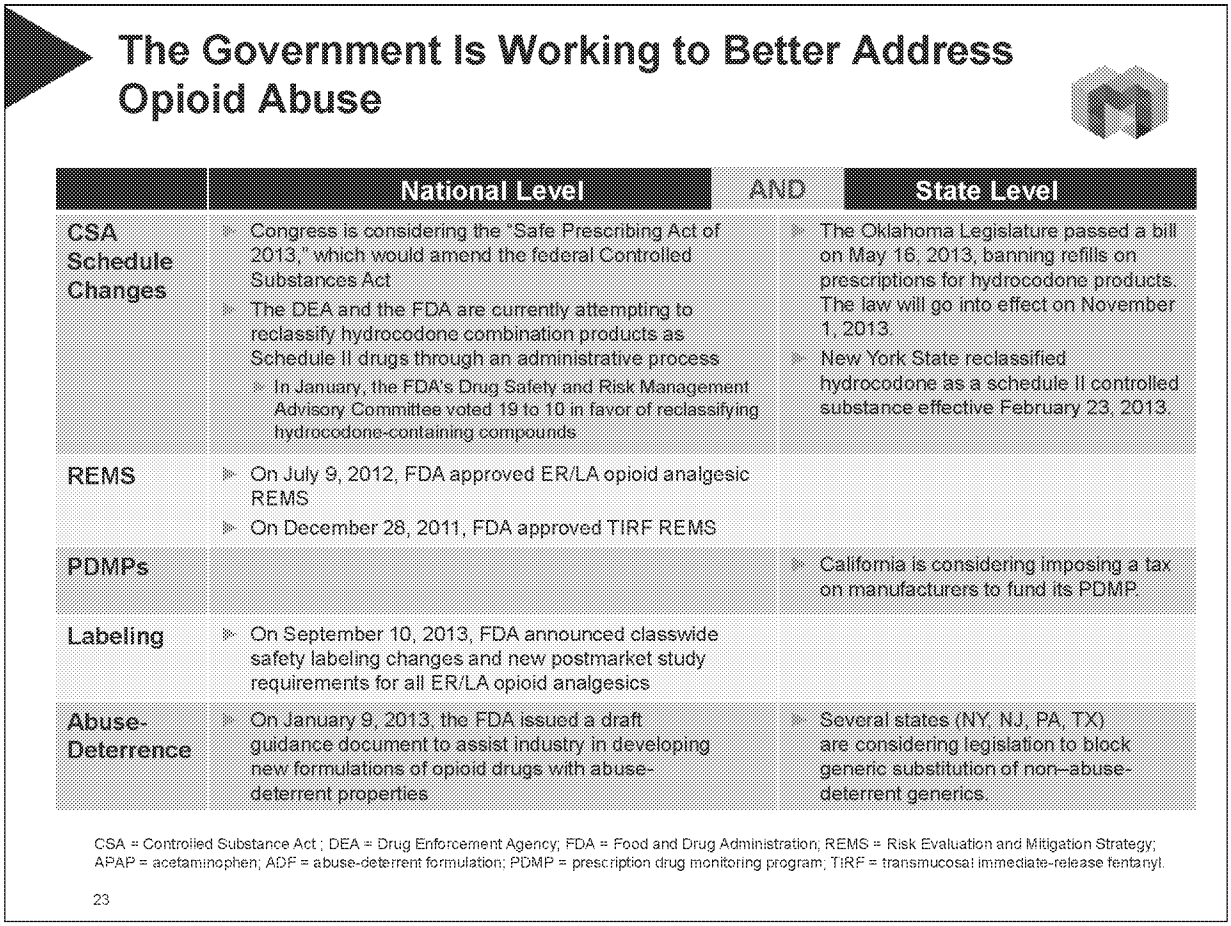

The Government Is Working to Better Address Opioid Abuse

	National Level	AND	State Level
CSA Schedule Changes	▸ Congress is considering the "Safe Prescribing Act of 2013," which would amend the federal Controlled Substances Act ▸ The DEA and the FDA are currently attempting to reclassify hydrocodone combination products as Schedule II drugs through an administrative process ▸ In January, the FDA's Drug Safety and Risk Management Advisory Committee voted 19 to 10 in favor of reclassifying hydrocodone-containing compounds		▸ The Oklahoma Legislature passed a bill on May 16, 2013, banning refills on prescriptions for hydrocodone products. The law will go into effect on November 1, 2013. ▸ New York State reclassified hydrocodone as a schedule II controlled substance effective February 23, 2013.
REMS	▸ On July 9, 2012, FDA approved ER/LA opioid analgesic REMS ▸ On December 28, 2011, FDA approved TIRF REMS		
PDMPs			▸ California is considering imposing a tax on manufacturers to fund its PDMP
Labeling	▸ On September 10, 2013, FDA announced classwide safety labeling changes and new postmarket study requirements for all ER/LA opioid analgesics		
Abuse-Deterrence	▸ On January 9, 2013, the FDA issued a draft guidance document to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties		▸ Several states (NY, NJ, PA, TX) are considering legislation to block generic substitution of non–abuse-deterrent generics.

CSA = Controlled Substance Act ; DEA = Drug Enforcement Agency; FDA = Food and Drug Administration; REMS = Risk Evaluation and Mitigation Strategy; APAP = acetaminophen; ADF = abuse-deterrent formulation; PDMP = prescription drug monitoring program; TIRF = transmucosal immediate-release fentanyl.

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At the national and state levels, there are several initiatives in place, including: Controlled Substance Act (CSA), abuse deterrence, REMS and PDMPs. The US Congress, Drug Enforcement Agency, and Food and Drug Administration are currently considering changes to reclassify hydrocodone products as class II substances.1 New York State has already accomplished this.2 In Oklahoma, prescriptions for hydrocodone products may not be refilled as of November 1, 2013.3 On a national level, in 2011 the White House announced a comprehensive plan designed to address the public health impact of misuse and abuse of prescription pain medications.4,5 The FDA issued new Industry Guidance for Abuse-Deterrent Opioids – Evaluation and Labeling.6 Manufacturers of long-acting and extended-release opioid formulations are required to provide a Risk Evaluation and Mitigation Strategy (REMS).4,5 State Prescription Drug Monitoring Programs (PDMPs) have been expanded.4,5 Also in 2011, the FDA requested manufacturers to limit the unit dose of acetaminophen to 325 mg.7 In 2012, Washington State instituted a requirement for physicians to refer chronic pain patients taking high doses of opioids for evaluation by pain specialists.8 New York State requires that physicians consult the PDMP database prior to prescribing controlled substances to identify “doctor-shoppers.”9

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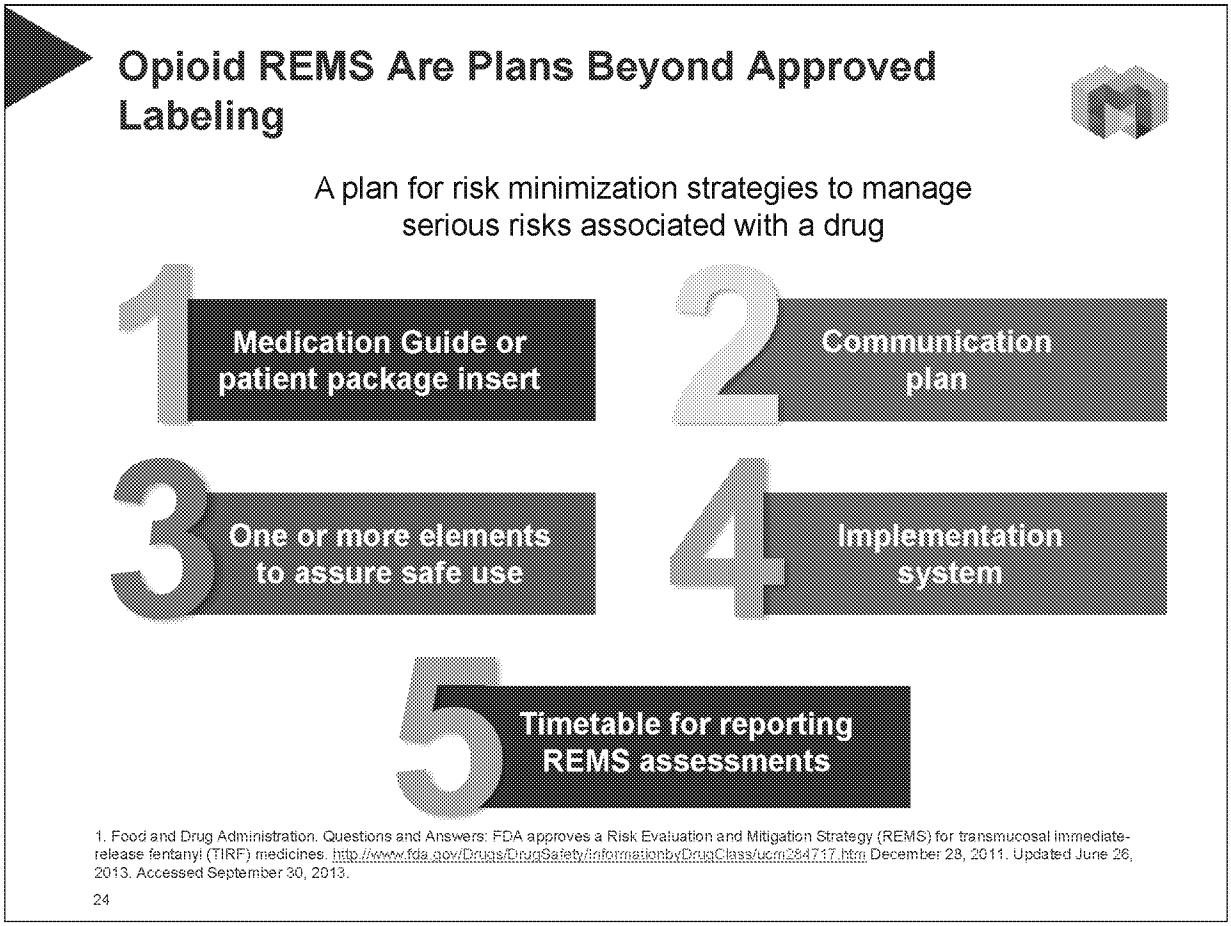

A Risk Evaluation and Mitigation Strategy (REMS) is a risk management plan that employs strategies to minimize risk beyond approved labeling, in order to manage serious risks that are associated with a drug. Under the FDA Amendments Act of 2007, the FDA is granted the authority to require manufacturers to develop a REMS when the FDA finds that a REMS program is necessary to ensure that a drug's benefits outweigh its risks. A REMS can include a Medication Guide or patient package insert, communication plan, at least one or more components to assure safe use, an implementation system and a timetable for submission of the REMS assessments.

References

1. Food and Drug Administration. Questions and Answers: FDA approves a Risk Evaluation and Mitigation Strategy (REMS) for transmucosal immediate-release fentanyl (TIRF) medicines. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm December 28, 2011. Updated June 26, 2013. Accessed September 30, 2013.

REMS is a risk management plan that uses risk minimization strategies beyond approved labeling to manage serious risks associated with a drug. Under the Food and Drug Administration Amendments Act of 2007, FDA has the authority to require a manufacturer to develop a REMS when FDA finds a REMS is necessary to ensure that the benefits of a drug outweigh its risks.

A REMS can include a Medication Guide or patient package insert, communication plan, one or more elements to assure safe use, an implementation system, and a timetable for submission of the REMS assessments

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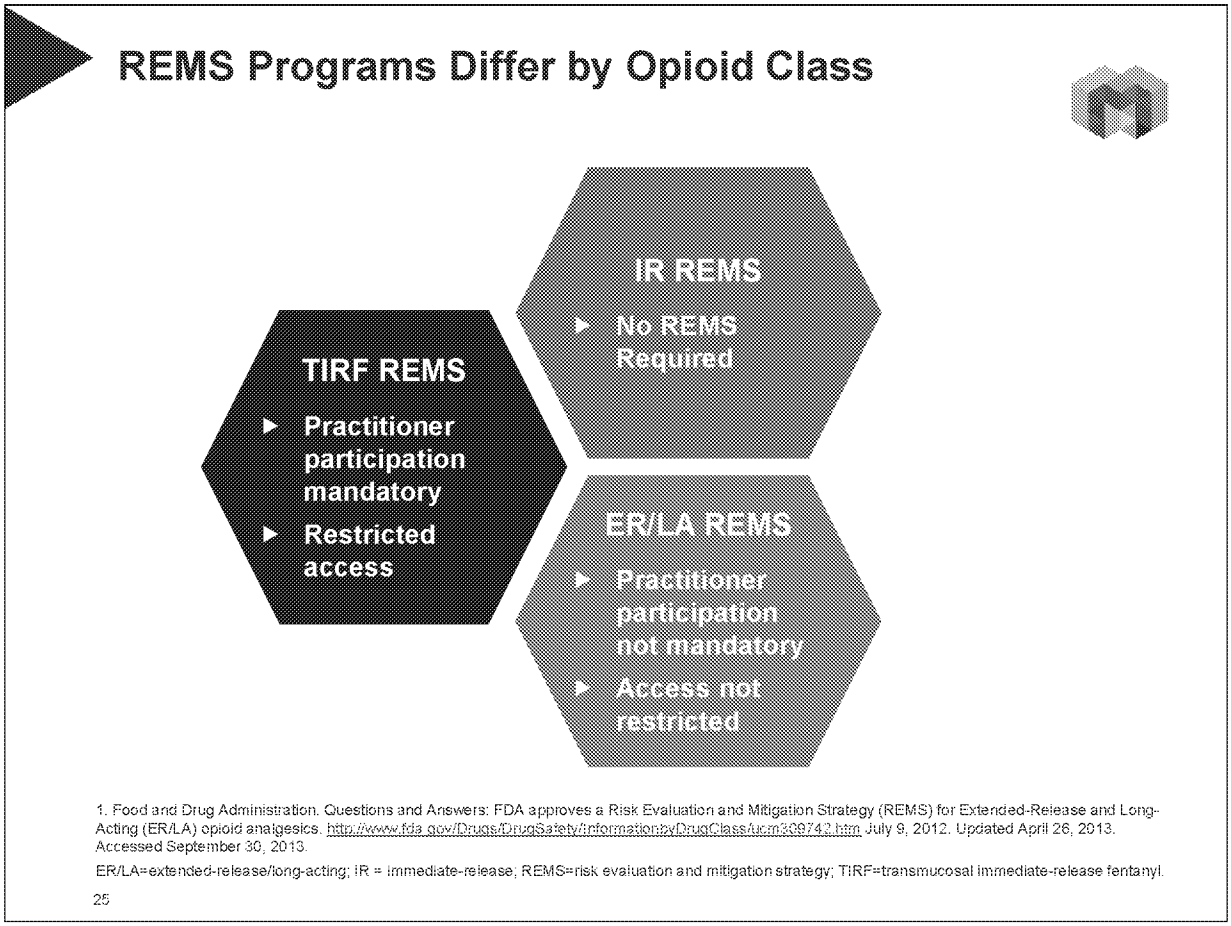
TIRF REMS p2 answer to Q2

TIRF REMS p2 answer to Q2

TIRF REMS p2 answer to Q2



REMS programs differ by class of opioid medication. Transmucosal immediate release fentanyl drugs are indicated for the management of breakthrough pain in cancer patients.1 To make it easier for healthcare providers, the FDA agreed to a single, shared-access risk evaluation and mitigation strategy for all drugs in the TIRF class. Healthcare providers who prescribe TIRF medicines for outpatient use are required to enroll in the TIRF REMS Access program. Prescribers will be required to re-enroll in the TIRF REMS program every 2 years from the date of enrollment into the TIRF REMS or from the date of enrollment into the individual REMS, whichever comes first. Patients who are prescribed TIRFs as outpatients are required to sign a Patient–Prescriber Agreement with their healthcare provider and will be asked to read the Medication Guide provided to them by their prescriber. Only outpatient and inpatient pharmacies that dispense TIRF medicines are required to enroll in the TIRF REMS Access program. Under the new class REMS, prescribers, pharmacies, distributors, and outpatients will need to enroll in only 1 REMS program — the TIRF REMS Access program — to prescribe, dispense, or receive all drugs in the TIRF medicines class.

REMS required for extended-release/long-acting opioids are less stringent than those for TIRF. Manufacturers are required to fund continuing medical education programs for practitioners and to provide patient counseling materials.2 However, the ER/LA opioid analgesics REMS training program will not include a mandatory requirement linked to allowing healthcare professionals to prescribe ER/LA opioid analgesics.

Because immediate release formulations contain smaller amounts of drug, there is no REMS requirement for these agents.2

References

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for transmucosal immediate-release fentanyl (TIRF) medicines.
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TIRF REMS p2 answer to Q1
TIRF REMS p2 answer to Q3
TIRF REMS p3 answer to Q6
TIRF REMS p4 answer to Q8
TIRF REMS p3 answer to Q7
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ER/LA REMS p 3 answer to Q5
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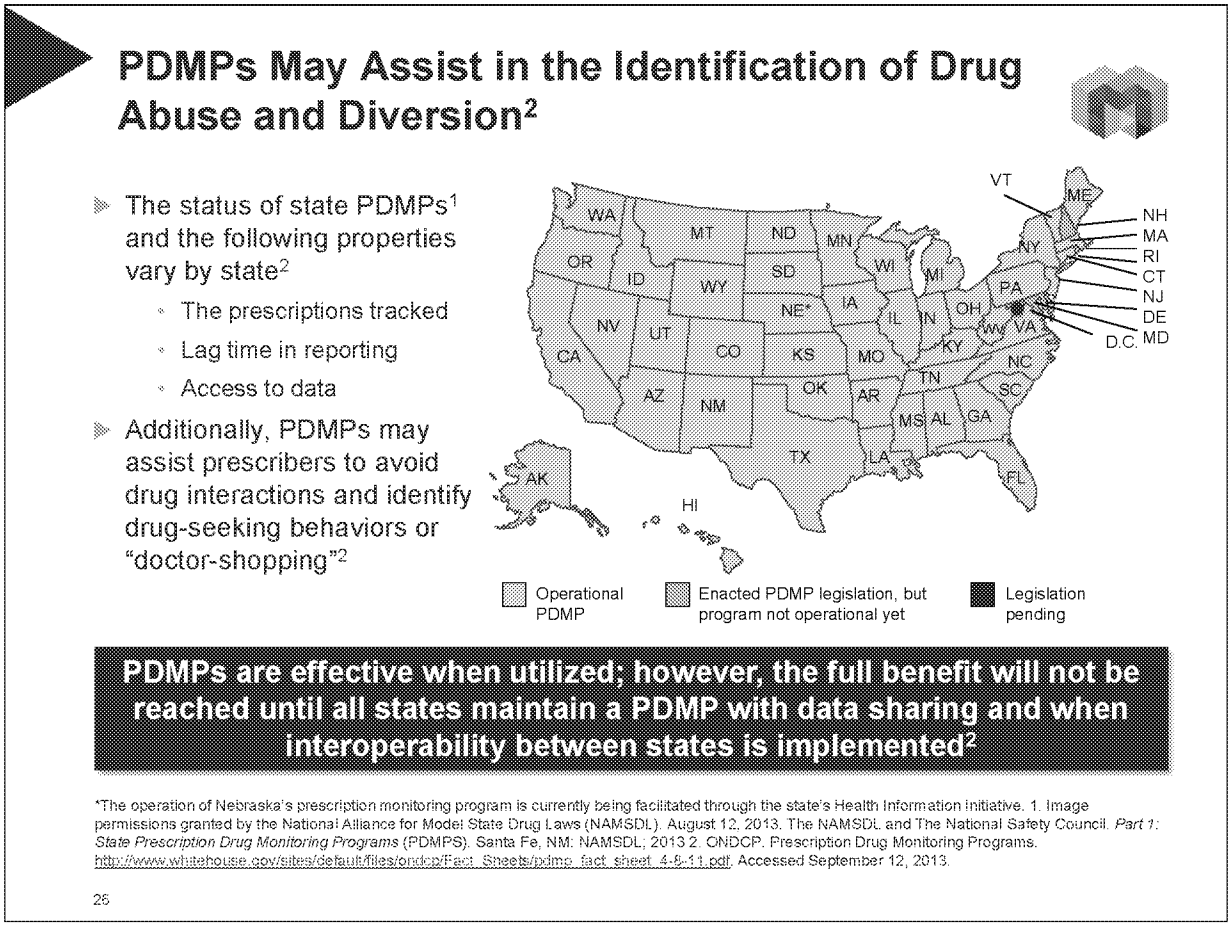

The majority of the states have active PDMPs that may assist in the identification of drug abuse and diversion, with the rest to follow. The status of PDMPs varies by state and by the prescriptions tracked, lag time in reporting of information, and access to data. PDMPs may provide an additional benefit to prescribers in providing information to avoid drug interactions and identify patients with drug-seeking or "doctor-shopping" behaviors. Unfortunately, the full benefit of these programs may not be realized until information can be communicated between states with PDMPs.

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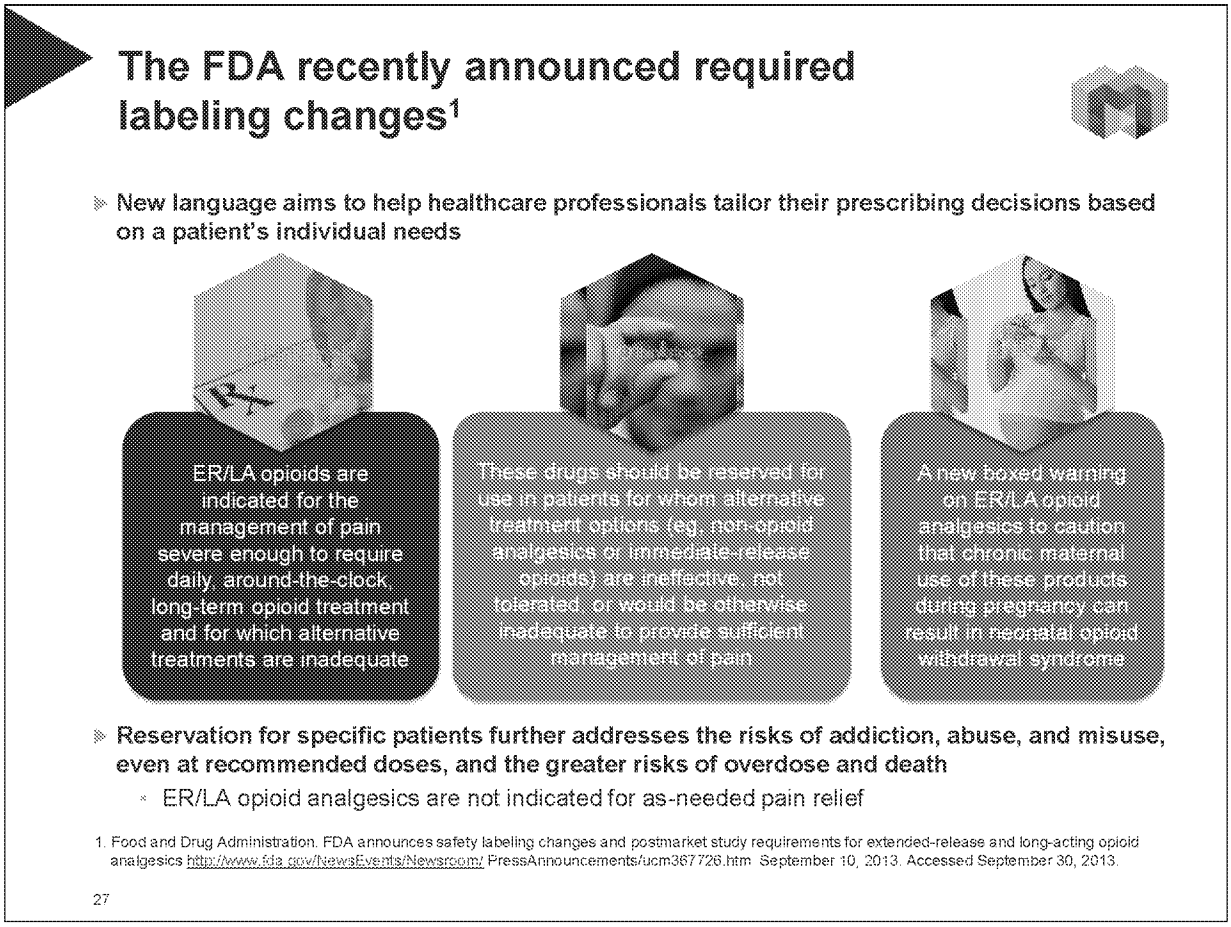

In order to facilitate better prescribing of ER/LA opioids, the FDA required changes to labeling based on the needs of the individual patient. New labeling requirements for ER/LA products address the following: the management of pain sufficiently severe to require 24-hour continuous long-term opioid treatment for which alternative treatment is inadequate; patients for whom alternative treatment is ineffective, not tolerated or would be otherwise inadequate; chronic maternal use of ER/LA opioids during pregnancy. Further labeling requirements address the risks of addiction, abuse and misuse, even at recommended doses, the greater risks of overdose and death, and the fact that ER/LA opioids are not indicated for PRN prescribing.

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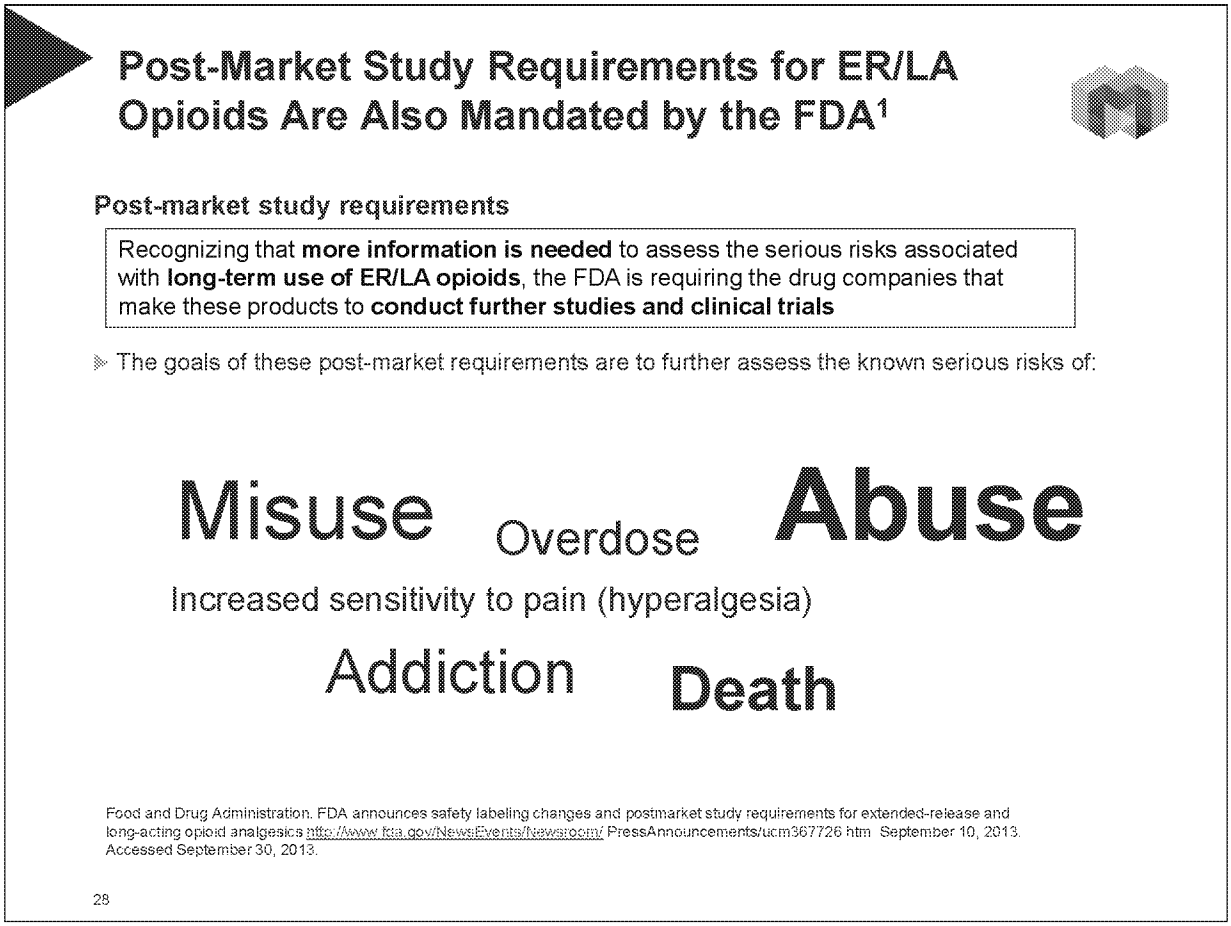

The FDA will also require the continued study and conducting of clinical trials on ER/LA opioids after they have begun to be marketed, realizing that more information is needed to assess the full effects of long-term use. The purpose of these studies is to assess the risks of misuse, overdose, abuse, hyperalgesia and addiction, and to assess opioid-related death.

References

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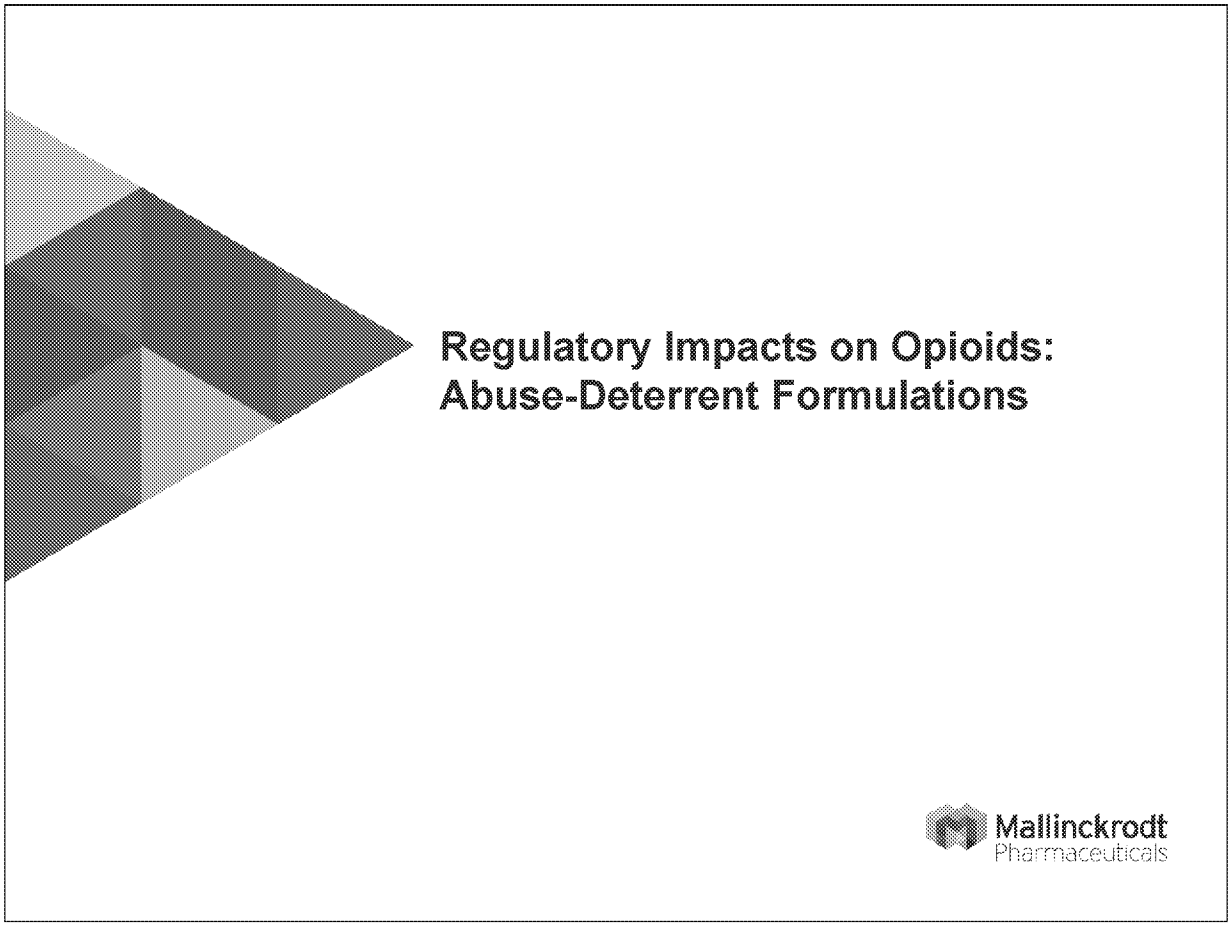
Regulatory Impacts on Opioids:
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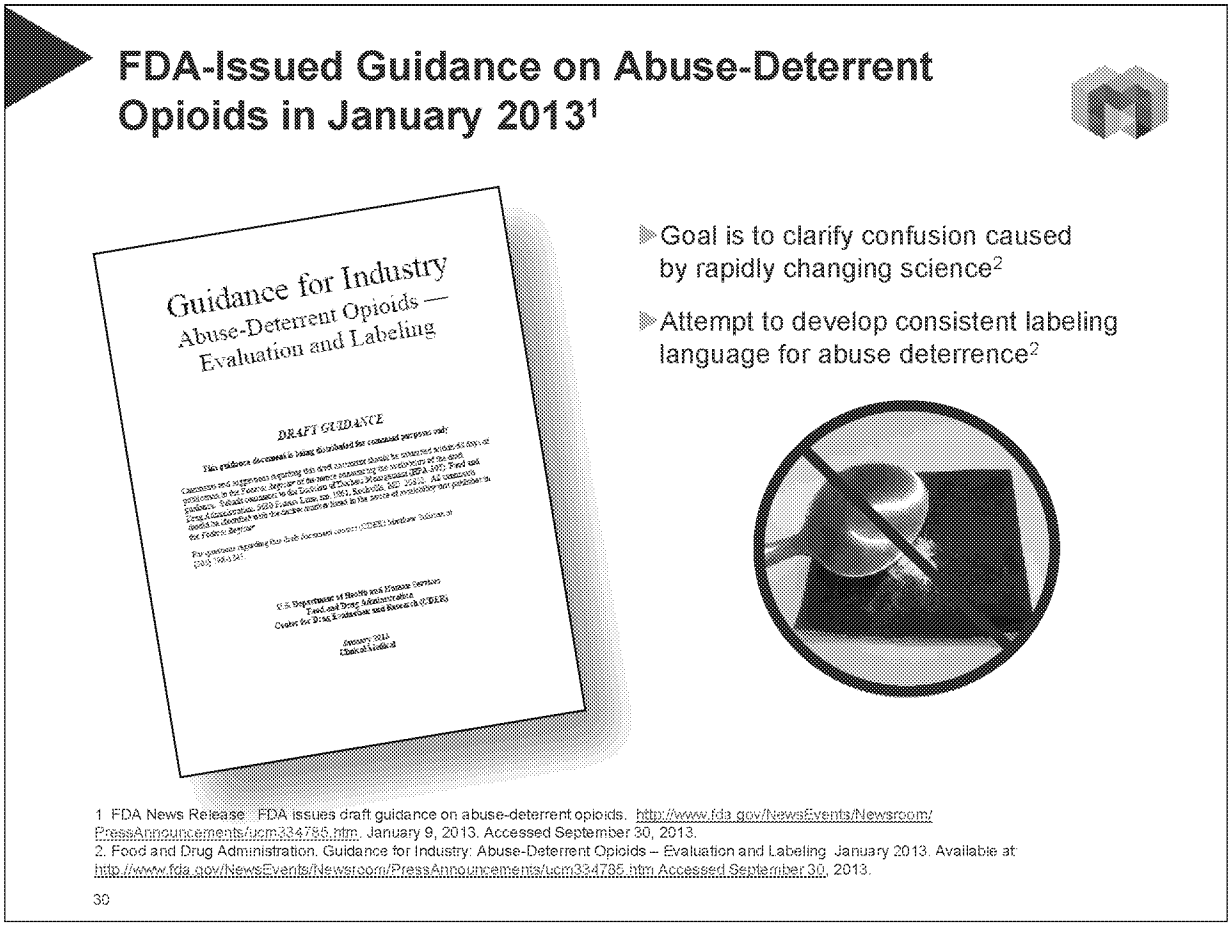

In January 2013, the FDA issued industry guidance regarding the development of opioid formulations that are more difficult to abuse or misuse.1

Abuse-deterrent formulations, as the name implies, make abuse more difficult. Recently, the FDA released a guidance statement pertaining to the evaluation and labeling of certain abuse deterrent formulations.2 Tamper-resistant formulations, for example, are designed to prevent destruction of controlled-release properties that would otherwise allow snorting or injection of more potent drug that is also more likely to be lethal. Other formulations utilize the addition of an antagonist to reduce euphoria; one of the main addictive properties of opioids. The addition of noxious substances to a drug is another method to prevent abuse. The use of a prodrug that requires metabolism to become active is another deterrent methodology that can be employed. Depot formulations by design release drug more slowly through, for example, intramuscular injection.

References

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http://www.hcplive.com/publications/pain-management/2011/december-2011/Abuse-deterrent-Technologies-in-Opioid-Medications-A-New-Weapon-in-the-Fight-against-Misuse-and-Abuse

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FDA 2013 p.2 L71-96

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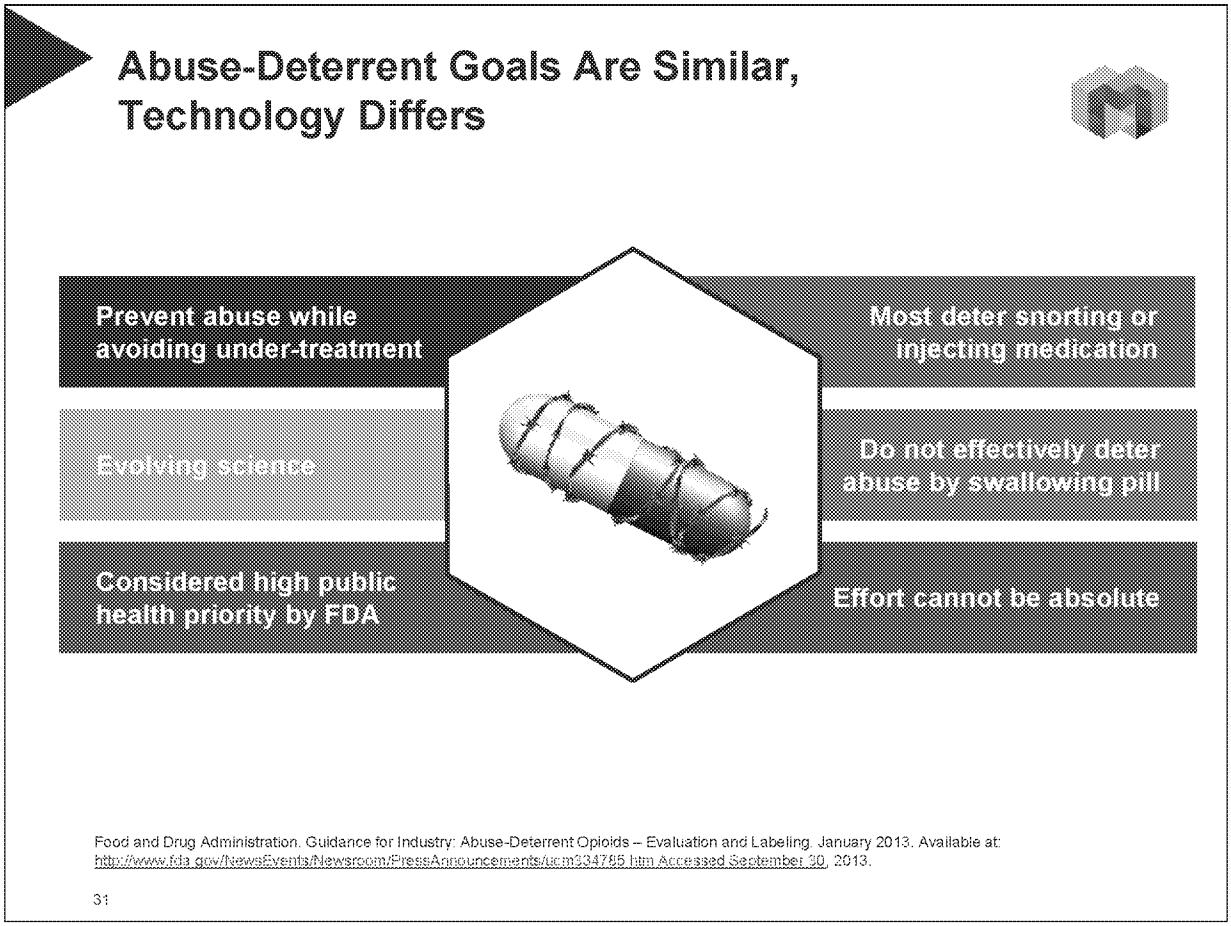

The objective of abuse deterrence is to prevent abuse without jeopardizing access to adequate pain relief. The science and technology are in their early stages of development. Although the FDA sees abuse as a public health problem, its guidance for industry is flexible to accommodate the evolving science.

Most abuse-deterrent technologies are designed to make it more difficult for medications to be abused using unintended routes of administration such as snorting or injection. However, oral administration represents the most widely used method of abuse, according to our research on oxycodone. Existing technologies do not deter individuals from swallowing multiple tablets or capsules to achieve a euphoric state.

References

Food and Drug Administration. Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. January 2013. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm Accessed September 30, 2013.

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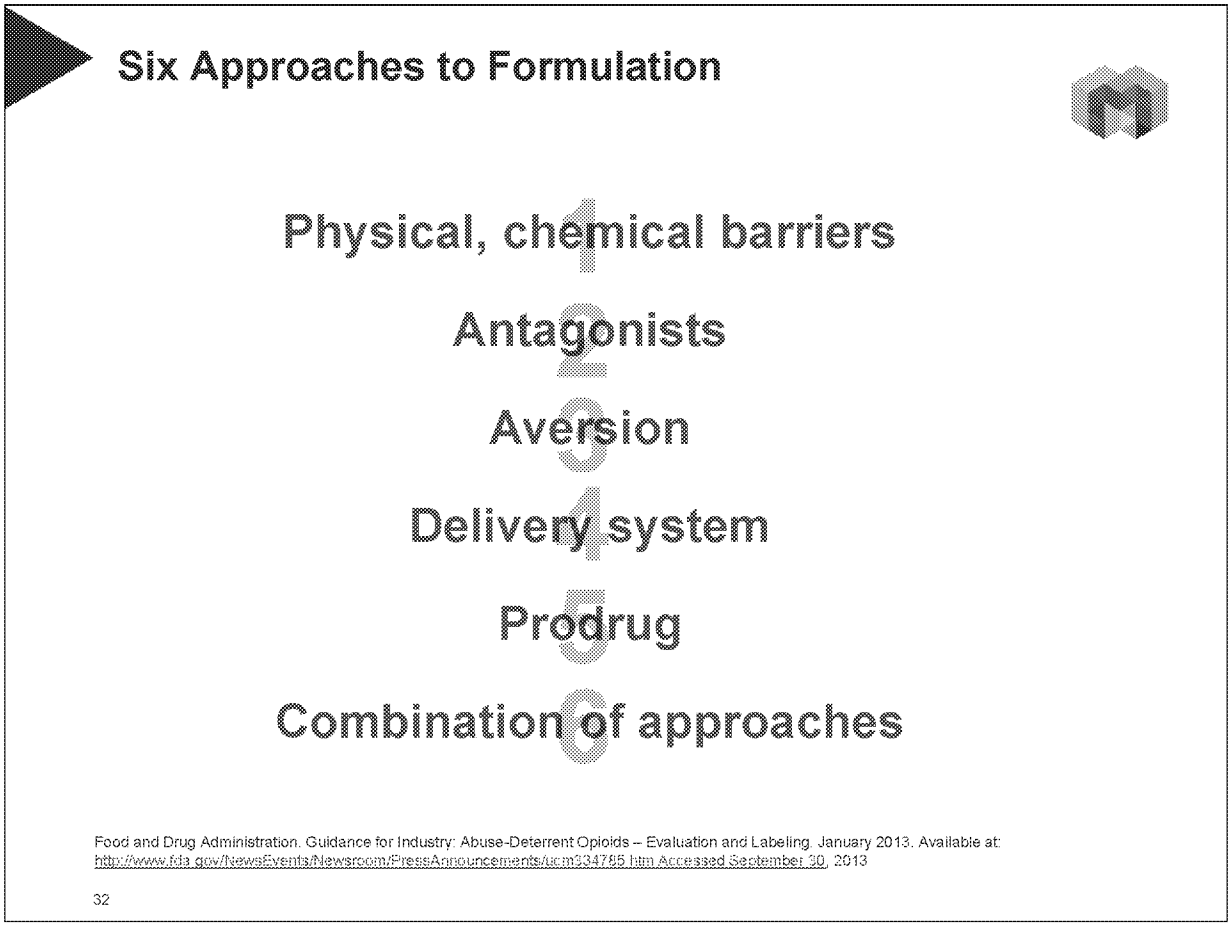

There are 5 approaches to developing abuse deterrent formulations, with the sixth being a combination of approaches.
The approaches to developing abuse deterrent formulations are:
Physical or chemical barriers to extraction of large volumes of opioids
Addition of antagonists that blunt the euphoria that is one of the main addictive properties of opioids
Addition of noxious substances to make ingestion aversive
Development of delivery systems, including depot injectable formulations and implants — certain drug-release designs or the method of drug delivery can offer resistance to abuse
Development of prodrugs that require physiological conversion to become active
Use of more than one approach at a time

References

Food and Drug Administration. Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. January 2013. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm Accessed September 30, 2013.
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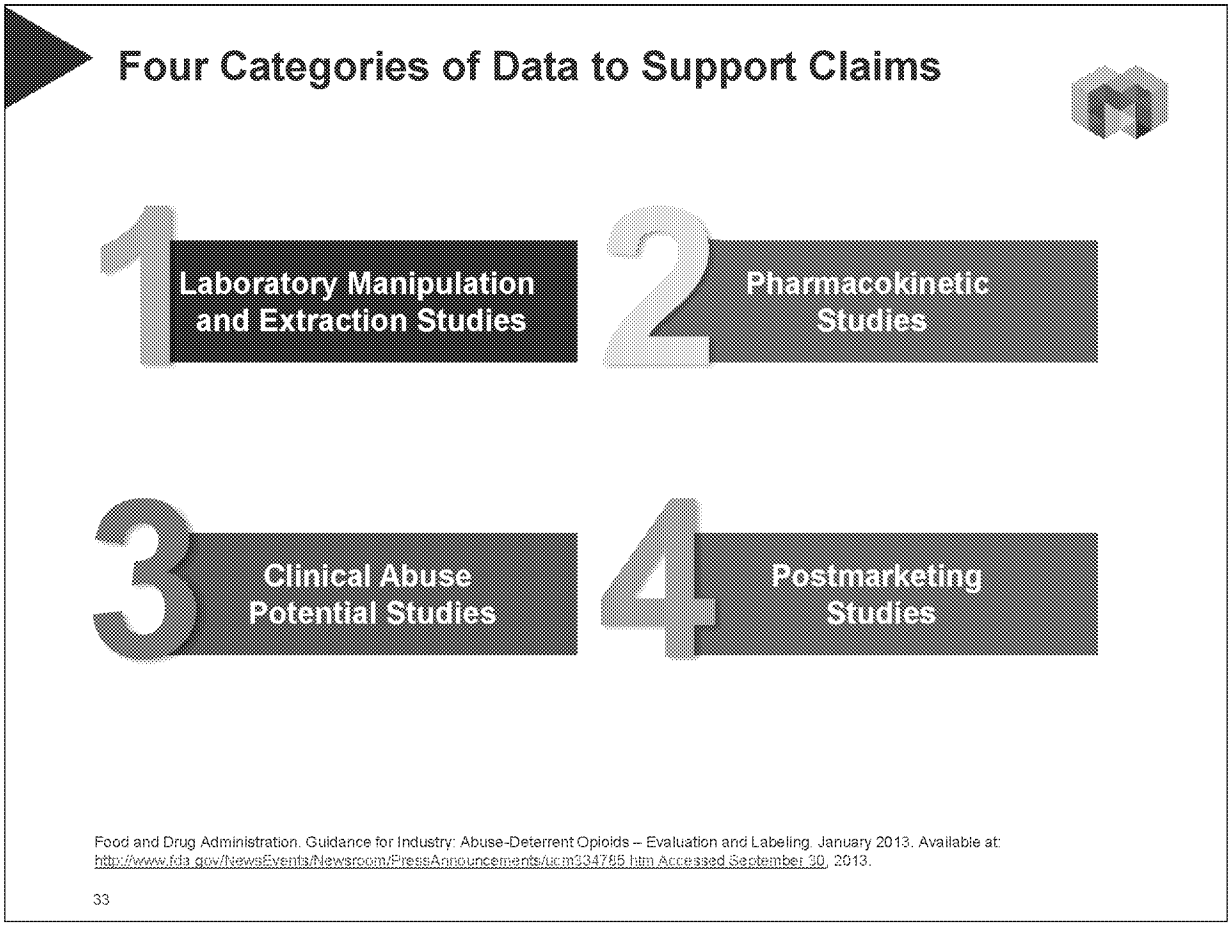
Food and Drug Administration. Guidance for industry: Abuse-Deterrent opioids – evaluation and labeling. January 2013.
Abuse deterrent guidance p 2 Section III



It is important to recognize that the first 3 categories of evidence can be completed prior to going to market. They demonstrate abuse liability in controlled conditions. Category 4 is always a postmarketing evaluation to assess the potential for abuse in real-world settings.

References

Food and Drug Administration. Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. January 2013. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm Accessed September 30, 2013.

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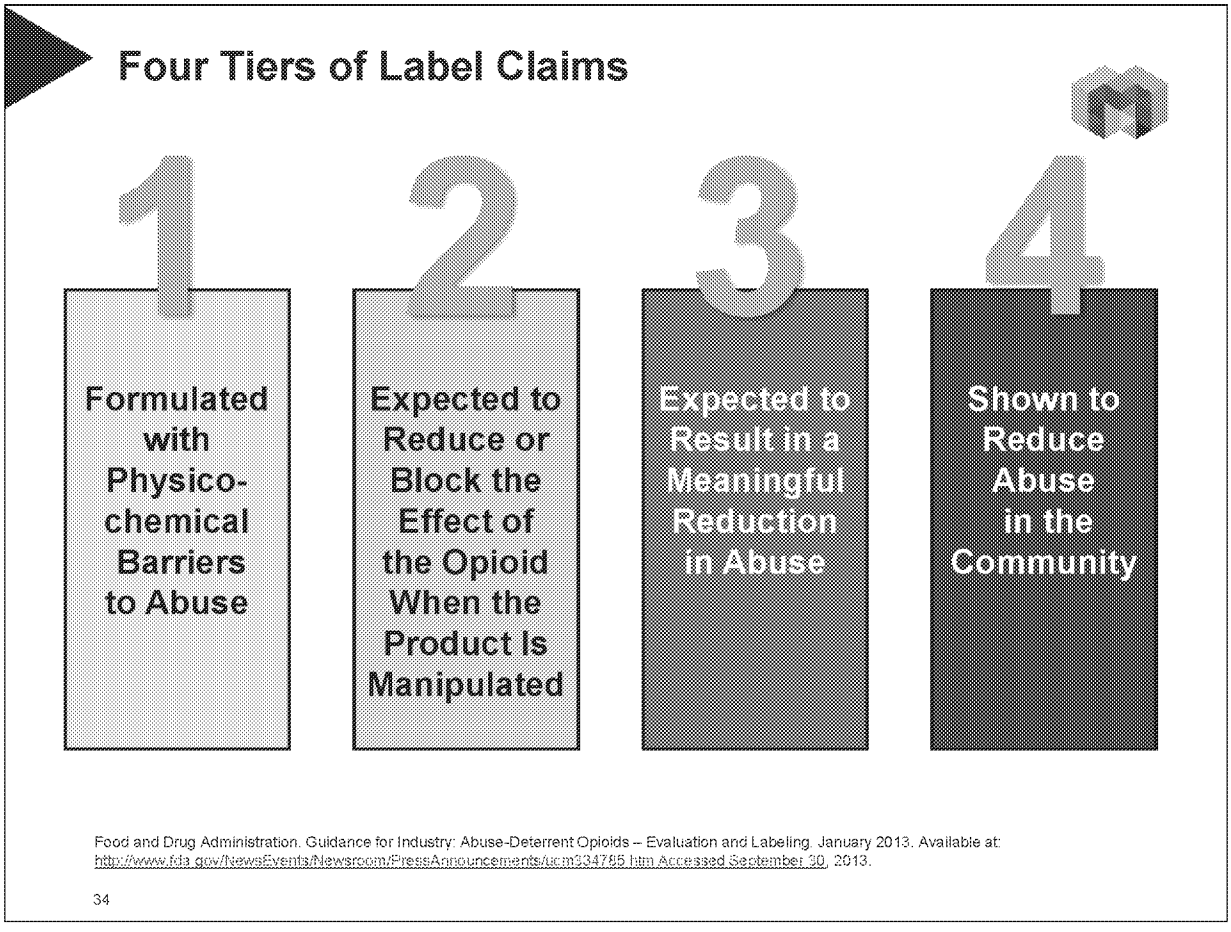
Abuse deterrent guidance p 2 L113-122

p. 13 L524-538

Food and Drug Administration. Guidance for industry: Abuse-Deterrent opioids – evaluation and labeling. January 2013.

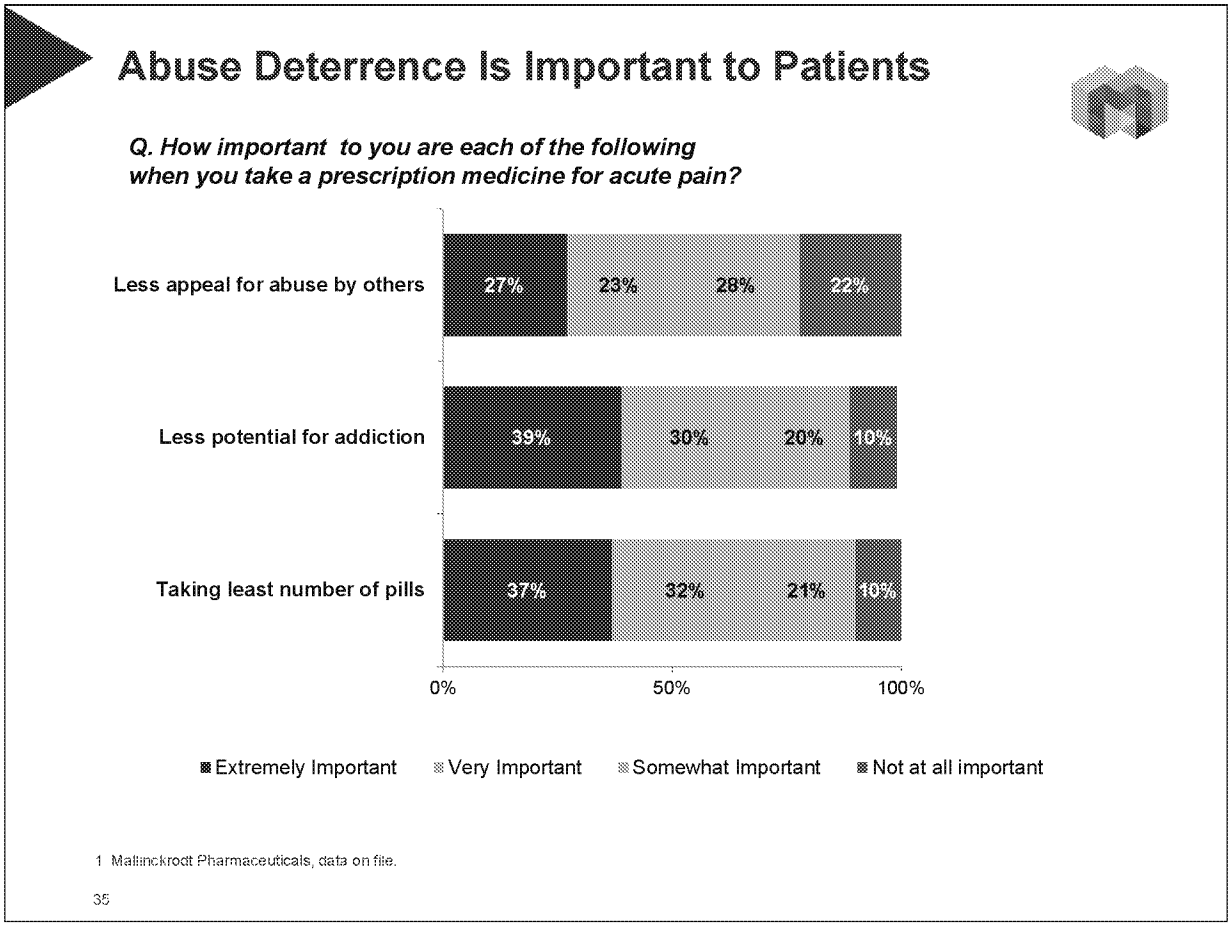


The 4 tiers of claims for abuse deterrence correlate with the categories of data to support the claims. However, the FDA generally expects data from categories 1 and 2 (and sometimes category 3) to substantiate a Tier 1 claim. Tier 4, demonstrated reduced abuse in the community, is a claim based on real-world, postmarketing experience.

References

Food and Drug Administration. Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. January 2013. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334785.htm Accessed September 30, 2013.

Food and Drug Administration. Guidance for industry: Abuse-Deterrent opioids – evaluation and labeling. January 2013.
Abuse deterrent guidance p 18 L707-721
Abuse deterrent guidance p 18 L707-721



The importance of abuse deterrence in pain medications is supported by the perceptions of patients. Less potential for addiction was extremely/very important for 39% of surveyed patients, almost the same percentage of whom ranked taking the least number of pills as extremely/very important.

Sixty-nine percent of surveyed patients strongly/somewhat agree that they would prefer a prescription pain medicine with characteristics that made it less appealing for misuse in their household.

References

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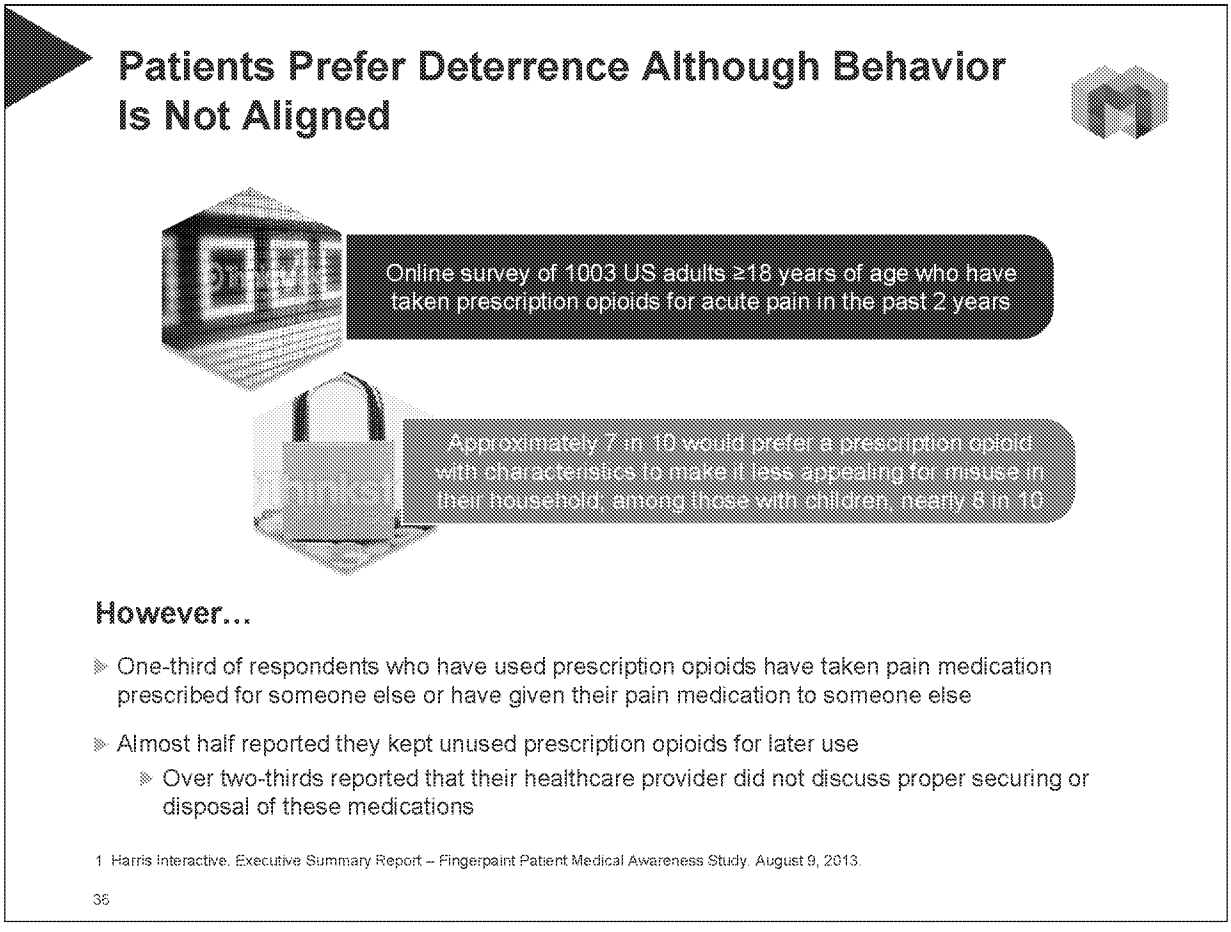
Omnibus Patient survey. Slide 10
Mallinckrodt Pharmaceuticals, data on file.



A very recent online survey was conducted from July 18 to July 29, 2013 of 1003 US adults ≥18 years of age who have taken prescription opioids for acute pain in the past 2 years. Interestingly, a majority of those surveyed (70-80%) expressed a desire to guard others in their household against drug misuse, while a significant percentage of participants, one-third, have also taken pain medication prescribed for someone else, or given their pain medication to someone else. Almost half admitted keeping their unused prescription opioids for later use and over two-thirds reported not having a discussion with their healthcare provider regarding securing or disposal of these medications.

References

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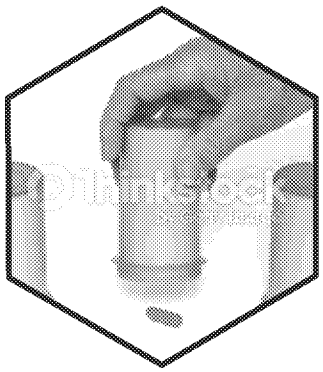
Summary

- Changes have been proposed to lower the maximum dose of acetaminophen and to potentially ban combination acetaminophen products
- Regulations have been promulgated clarifying abuse-deterrent opioid-formulation claims
- Abuse-deterrent formulations attempt to reduce abuse while avoiding under-treatment



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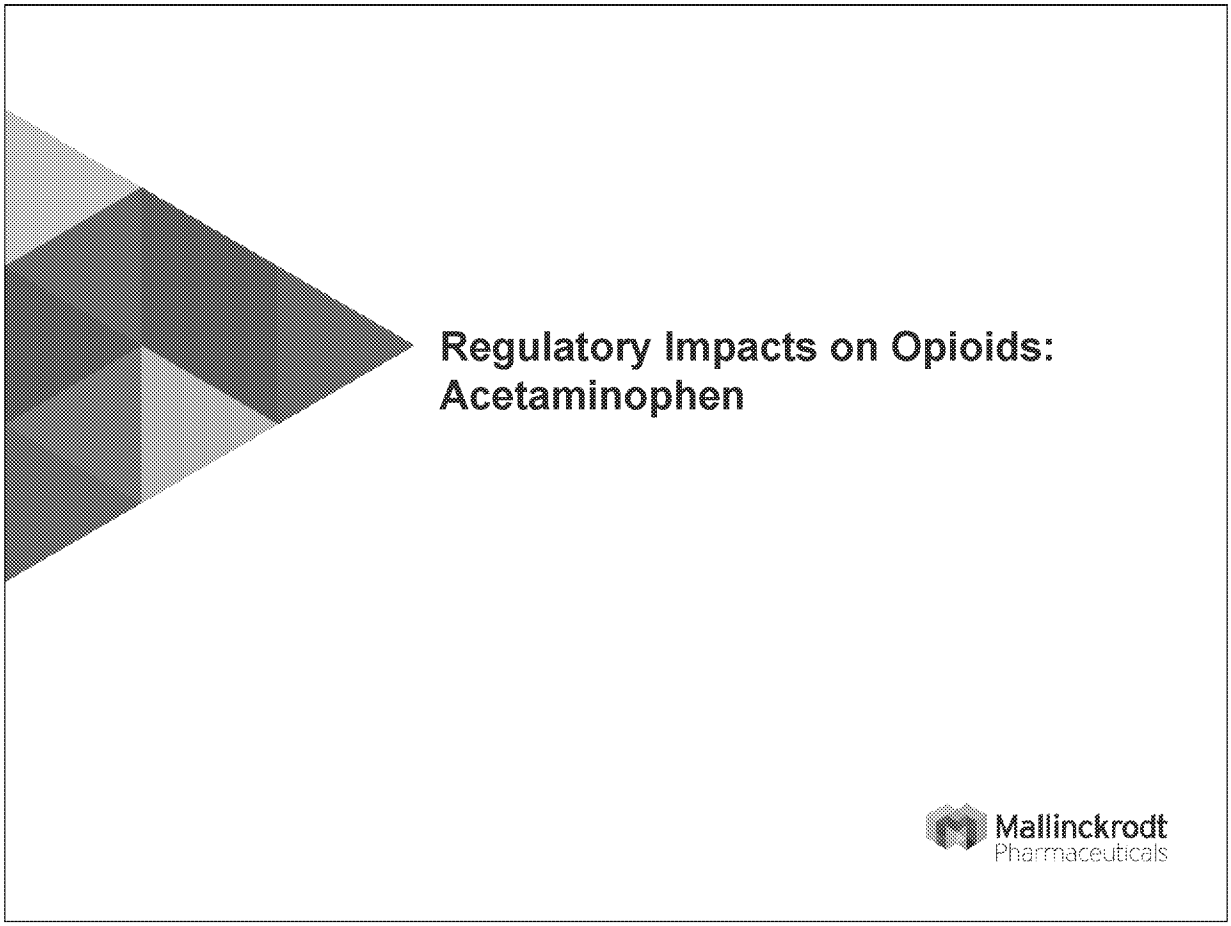
Regulatory Impacts on Opioids:
Acetaminophen
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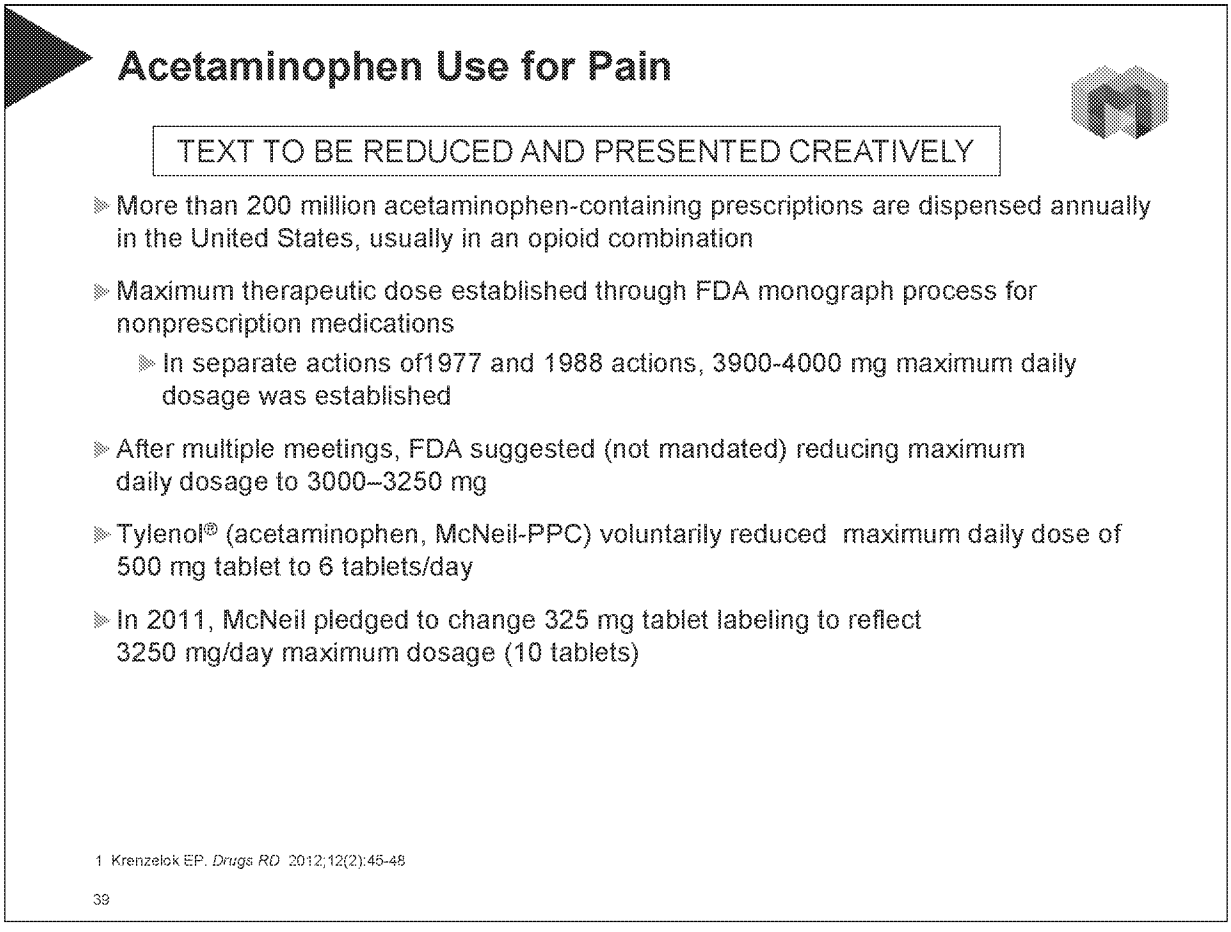
Pharmaceuticals

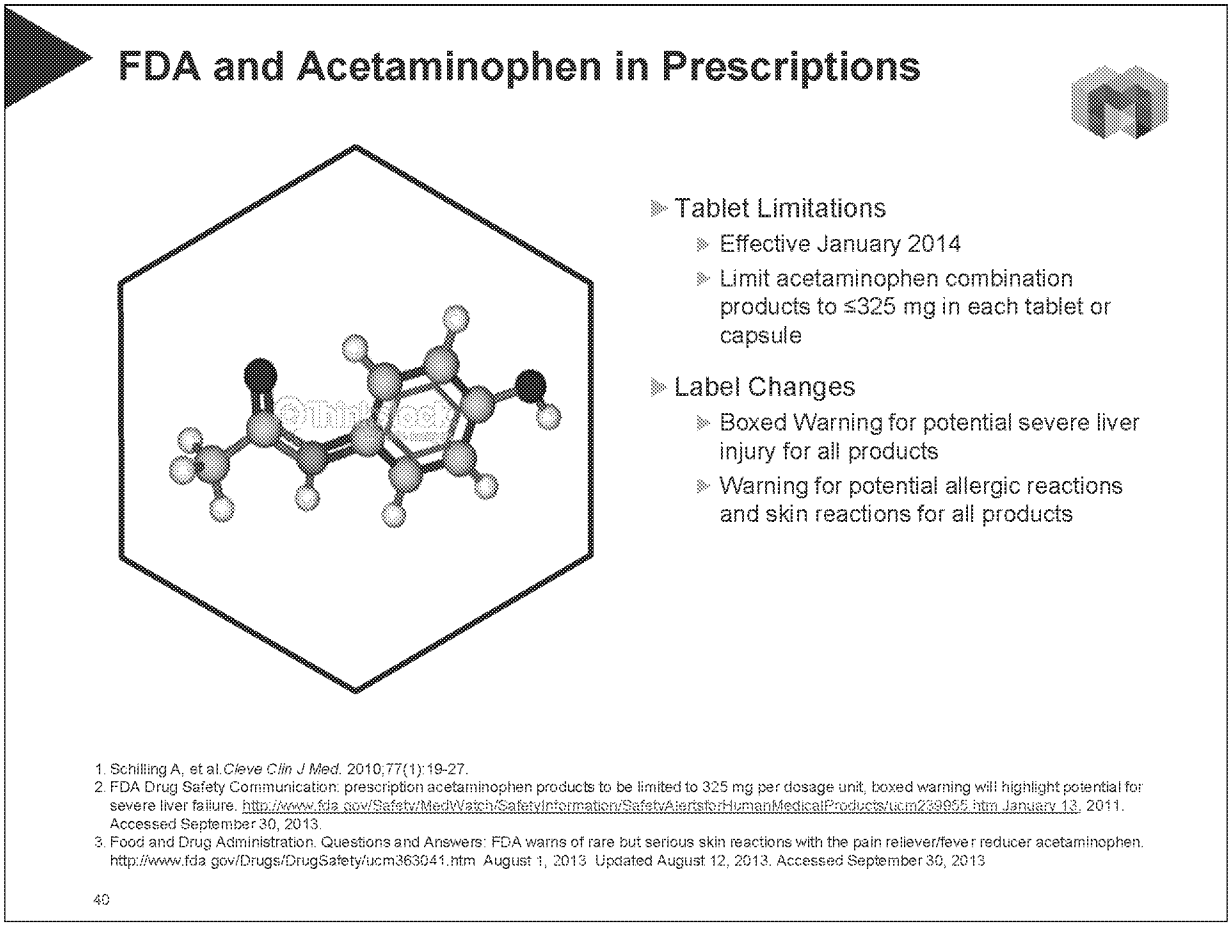


Long recognized as a safe and effective antipyretic and analgesic, acetaminophen is also associated with significant hepatotoxicity if taken inappropriately in excess of its recommended dosage. As explained above, for years the established maximum daily acetaminophen dosage stood at 4000 mg per day; however, the manufacturer of Tylenol® brand acetaminophen, McNeil, changed its labeling to reflect the new maximum dosage recommended by the FDA.

Generic manufacturers have remained consistent with the established monograph dosing and have not changed the dosing on their labels. It is inevitable that a great deal of confusion will result among both healthcare professionals and consumers about what is the correct and appropriate maximum daily acetaminophen dose.

References

1. Krenzelok EP, Royal MA. Confusion: acetaminophen dosing changes based on NO evidence in adults. Drugs R D. 2012;12(2):45-48.



Although acetaminophen is generally regarded as safe, in 2006, approximately 140,000 acetaminophen overdoses were reported in the United States. As many as half of these events were unintentional.1 Part of the reason for the high incidence is the widespread presence of acetaminophen in a range of prescription and over-the-counter products. Patients may take these agents together, which may result in liver damage.1

To lower the risk of unintentional overdose, the FDA now requires manufacturers of prescription combination products that contain acetaminophen to limit the amount of acetaminophen to no more than 325 mg in each tablet or capsule. In addition, a Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (eg, swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) are being added to the labels of all prescription drug products that contain acetaminophen.

The FDA is requiring that a warning about skin reactions be added to the labels of all prescription and OTC medicines containing acetaminophen. The skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) are rare but can be life-threatening when they do occur. The expectation is that by raising awareness of the rare possibility of these skin reactions, symptoms will be treated in time to prevent serious illness or death.

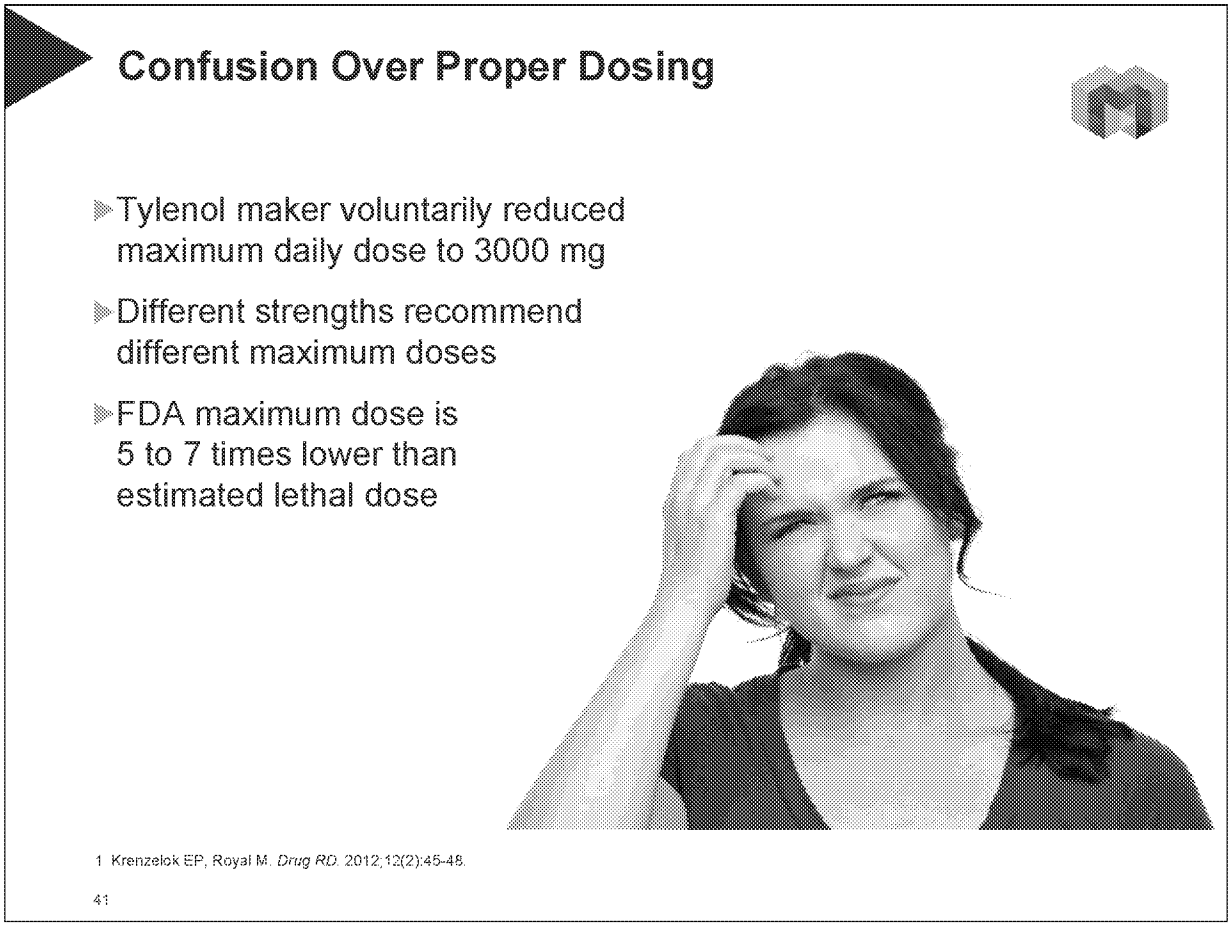
References

Schilling A, et al.Cleve Clin J Med. 2010;77(1):19-27.

FDA Drug Safety Communication: prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning will highlight potential for severe liver failure. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm239955.htm January 13, 2011. Accessed September 30, 2013.

Food and Drug Administration. Questions and Answers: FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen. http://www.fda.gov/Drugs/DrugSafety/ucm363041.htm August 1, 2013. Updated August 12, 2013. Accessed September 30, 2013.

TINA:
It may be beneficial to separate the tablet limitations from the label changes in the slides : we did, on the slide
No content restrictions were placed on the OTC formulations – only prescription : we specified prescription products, paragraph 2, line 1
Will need to describe the legislation regarding tablet limits is effective January 2014 : slide sub-bullet 1 under Tablet Limitations
Example image:
http://www.zmescience.com/other/science-abc/health-abc-acetaminophen-040402013/
Schilling, 2010. p 19 A&B; p 20 A&B
FDA Dose limit p 1A
FDA Dose limit p 2B, p 3A
FDA skin reaction p 1A
FDA Dose limit p 1A
FDA Dose limit p 2B, p 3A
FDA skin reaction p 1A



The FDA has conducted multiple advisory committee meetings to evaluate acetaminophen and its safety profile and has suggested (but not mandated) a reduction in the maximum daily dosage from 3900-4000mg to 3000-3250mg despite an absence of data showing that the lower dose was associated with lower rates of toxicity.

As many as 50% of individuals with acetaminophen hepatotoxicity have taken an intentional overdose. Risks associated with need to lower the daily dose include patients consuming daily alcohol and those with underlying hepatic disease. The makers of Tylenol (McNeil PPC) voluntarily lowered the maximum recommended daily dose, but for over-the-counter acetaminophen it remains at 4000 mg/day.

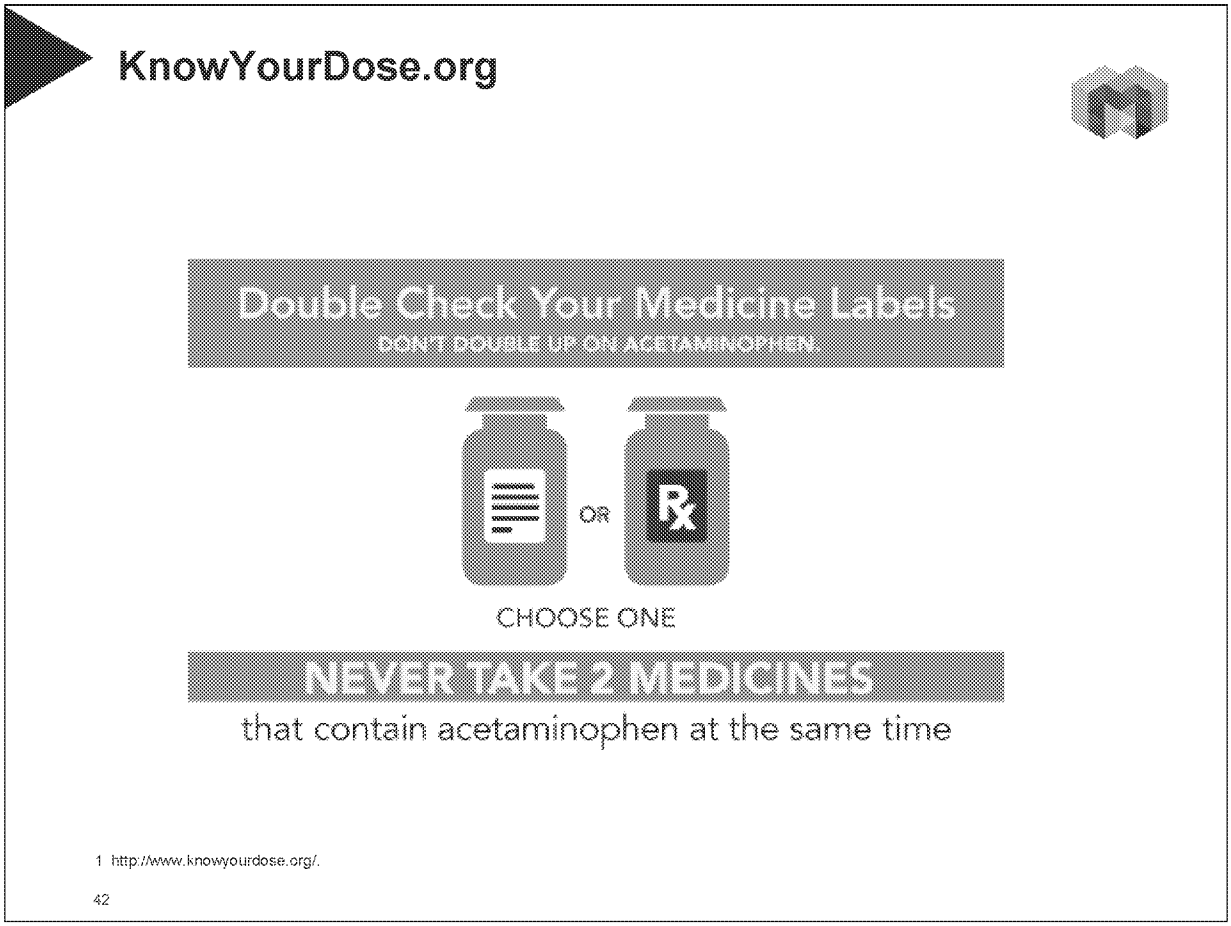
Manufacturers of generic acetaminophen have not changed their recommended dosing. These inconsistencies in recommended dosing have potential for patient confusion.

References

1. Krenzelok EP, Royal M. Confusion: Acetaminophen dosing changes based on NO evidence in adults. Drug RD. 2012;12(2):45-48.

Example image:
http://www.dynamic-bi.com/
Krenzelok 2012 p. 46 col 2 para 1 L9-13
Krenzelok 2012 p 47 col 1 para 3 L1-8;p. 46 col 1 para 1 L9-13
Krenzelok 2012 p. 46 col 2 para 3 L6-11
Krenzelok 2012 p 47 col 1 para 3 L9-10

Krenzelok 2012 p 47 col 1 para 3 L1-8; L11-12;p. 46 col 1 para 1 L9-13
Krenzelok 2012 p 47 col 1 para 3; L11-12
Krenzelok 2012 p 46 col 2 para 2; L1-10
Please note: I could not mark up Krenzelok
Krenzelok EP, Royal M. Confusion: Acetaminophen dosing changes based on NO evidence in adults. Drug RD. 2012;12(2):45-48.



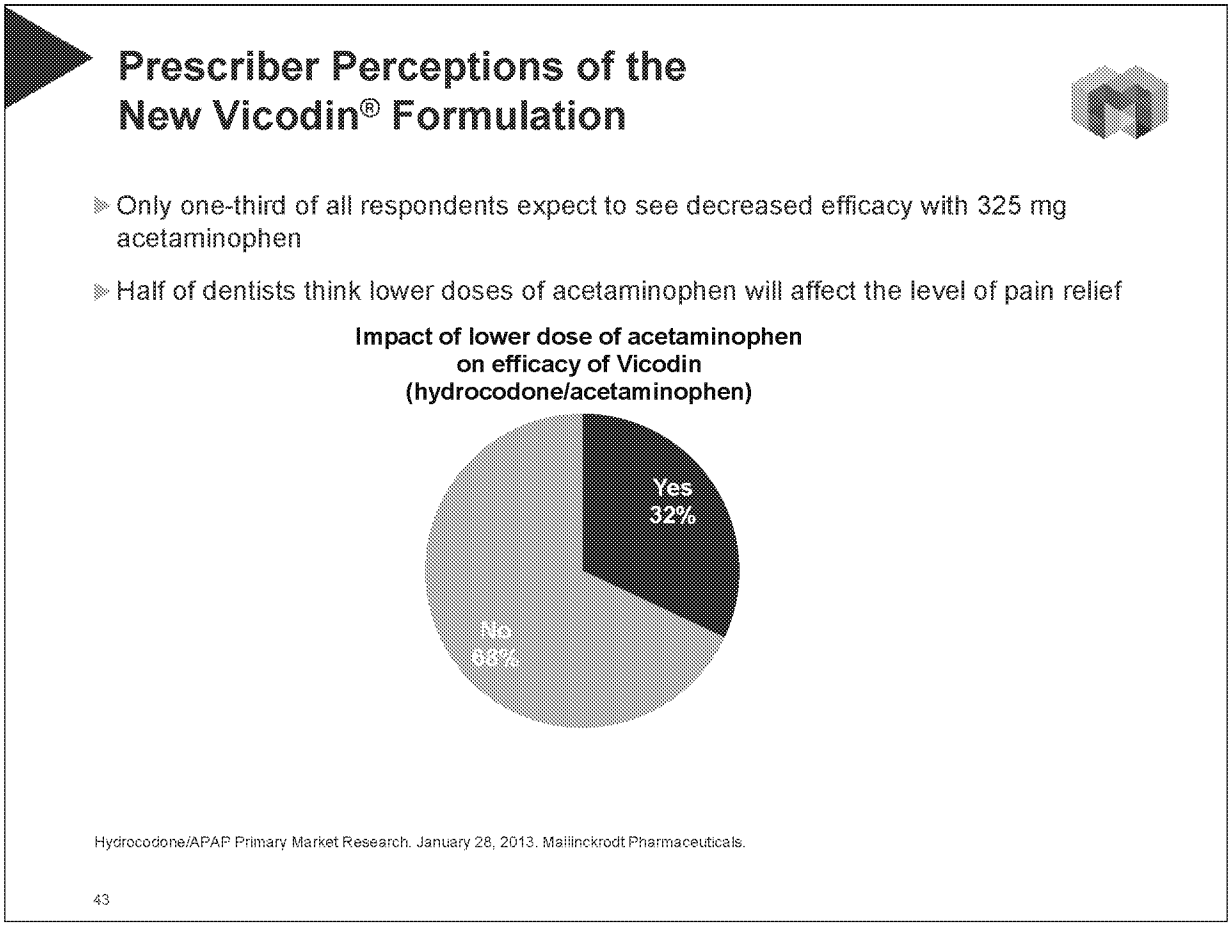
One challenge, particularly for patients, is to recognize the number of over-the-counter and prescription medications that contain acetaminophen. The Acetaminophen Awareness Coalition is a group representing consumer organizations, healthcare provider organizations, and health organizations that is attempting to educate patients and prescribers about using acetaminophen safely. Its Web site can be accessed at: KnowYourDose.org.

References

1. http://www.knowyourdose.org/

Example image:

http://www.dynamic-bi.com/



With respect to the new Vicodin® formulation, market research found that only 1 in 3 physicians expected that lower doses of acetaminophen in combination with an opioid would decrease efficacy. However, half of dentists were concerned about lower efficacy in pain relief.

References

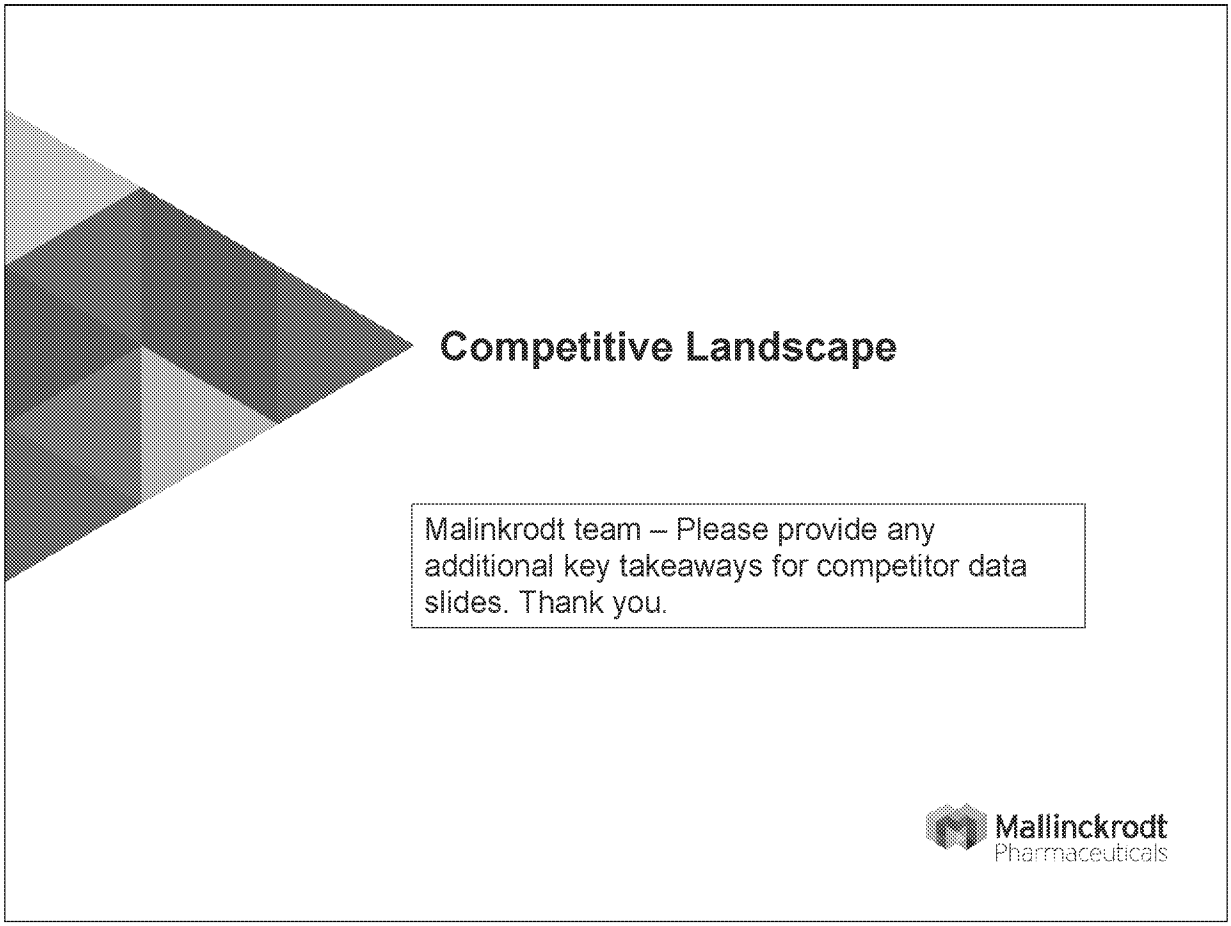
Hydrocodone/APAP Primary Market Research. January 28, 2013. Mallinckrodt Pharmaceuticals.

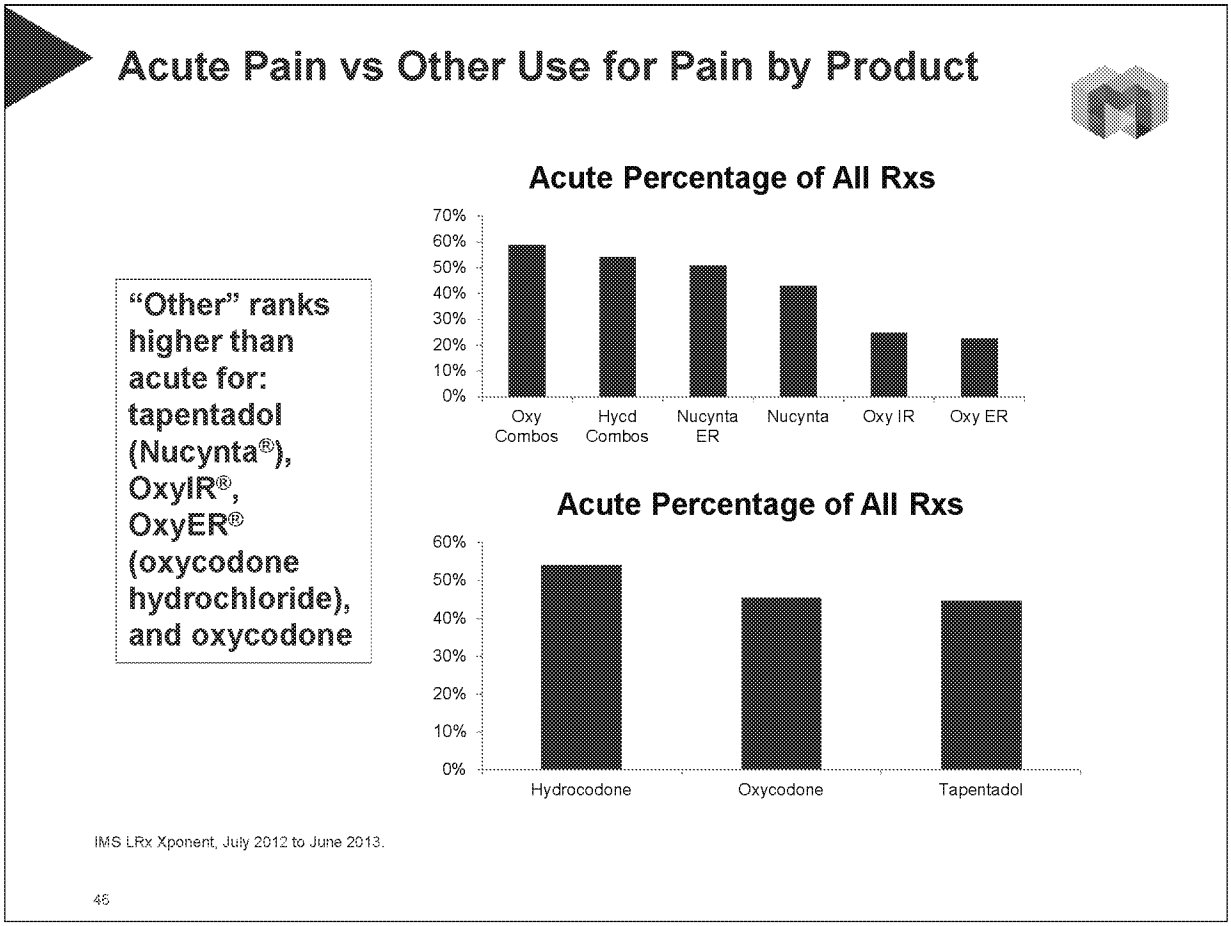
HYCD APAP slides slide #14

Mallinckrodt Pharmaceuticals, data on file.

Summary

- FDA is requiring lower doses of acetaminophen in combination products as well as warnings for hepatic injury, allergic reactions, and skin reactions
- Recommendations for maximum daily dose are inconsistent
- Most prescribers:
  - Do not anticipate that lowering acetaminophen content will affect efficacy of combination products
  - Do not expect to prescribe higher hydrocodone doses


Competitive Landscape
Malinkrodt team – Please provide any additional key takeaways for competitor data slides. Thank you.
Mallinckrodt Pharmaceuticals



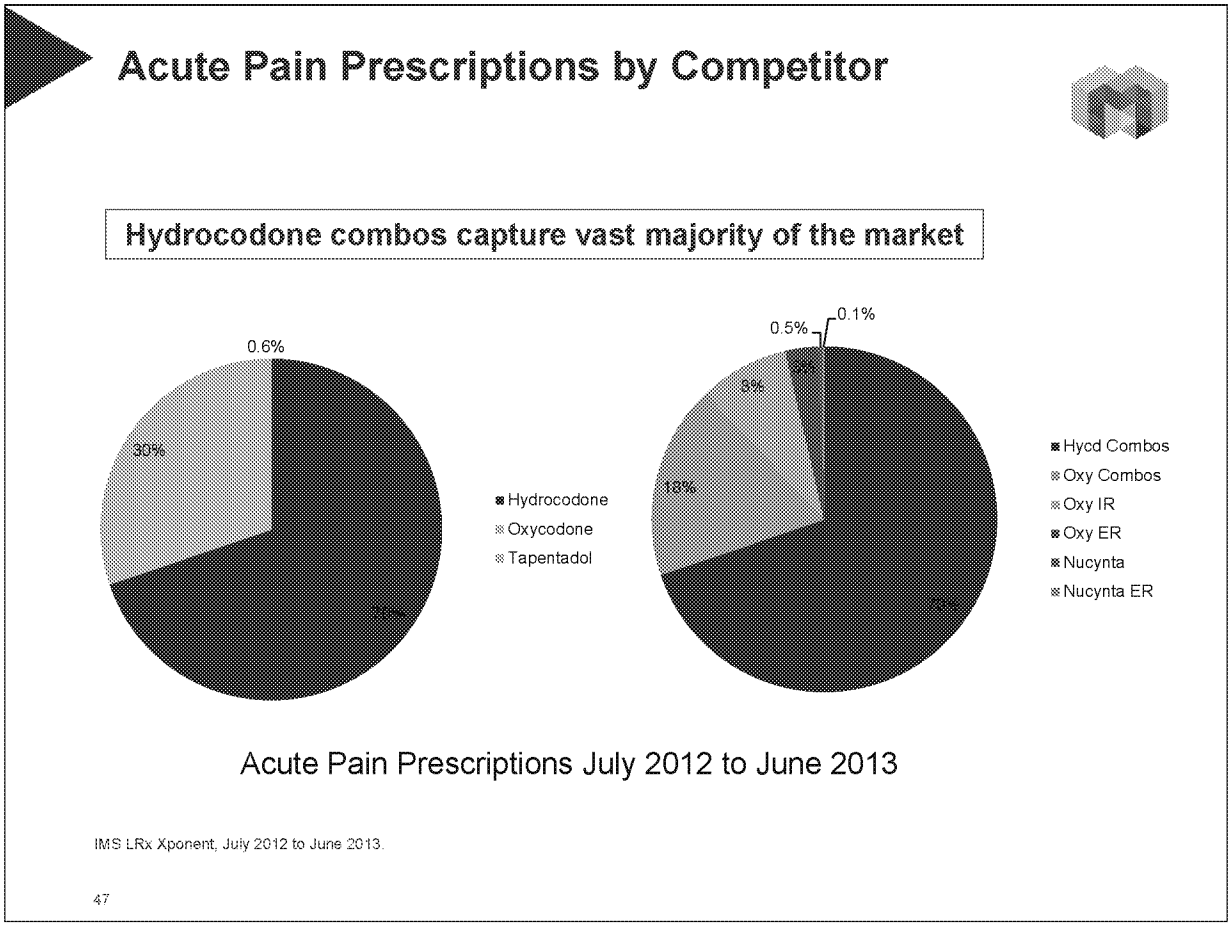
Prescriptions of competitor products can be viewed as the amount of prescriptions for acute pain compared with the amount for other use for pain. When use is viewed by each product and differentiated by molecule, “other” use ranks higher than acute use for tapentadol (Nucynta®), OxyIR®, OxyER® (oxycodone hydrochloride), and oxycodone. For use data for the “other” category see below.

Row LabelsAcute UseOther
Oxy Combos58.68%41%
Hycd Combos53.96%46%
Nucynta ER50.84%49%
Nucynta42.86%57%
Oxy IR24.88%75%
Oxy ER22.56%77%

Hydrocodone53.96%46%
Oxycodone45.44%55%
Tapentadol44.50%55%

See Excel: Acute Marketplace_Product,Specialty,Acute Percent.xlsx [Acute %]

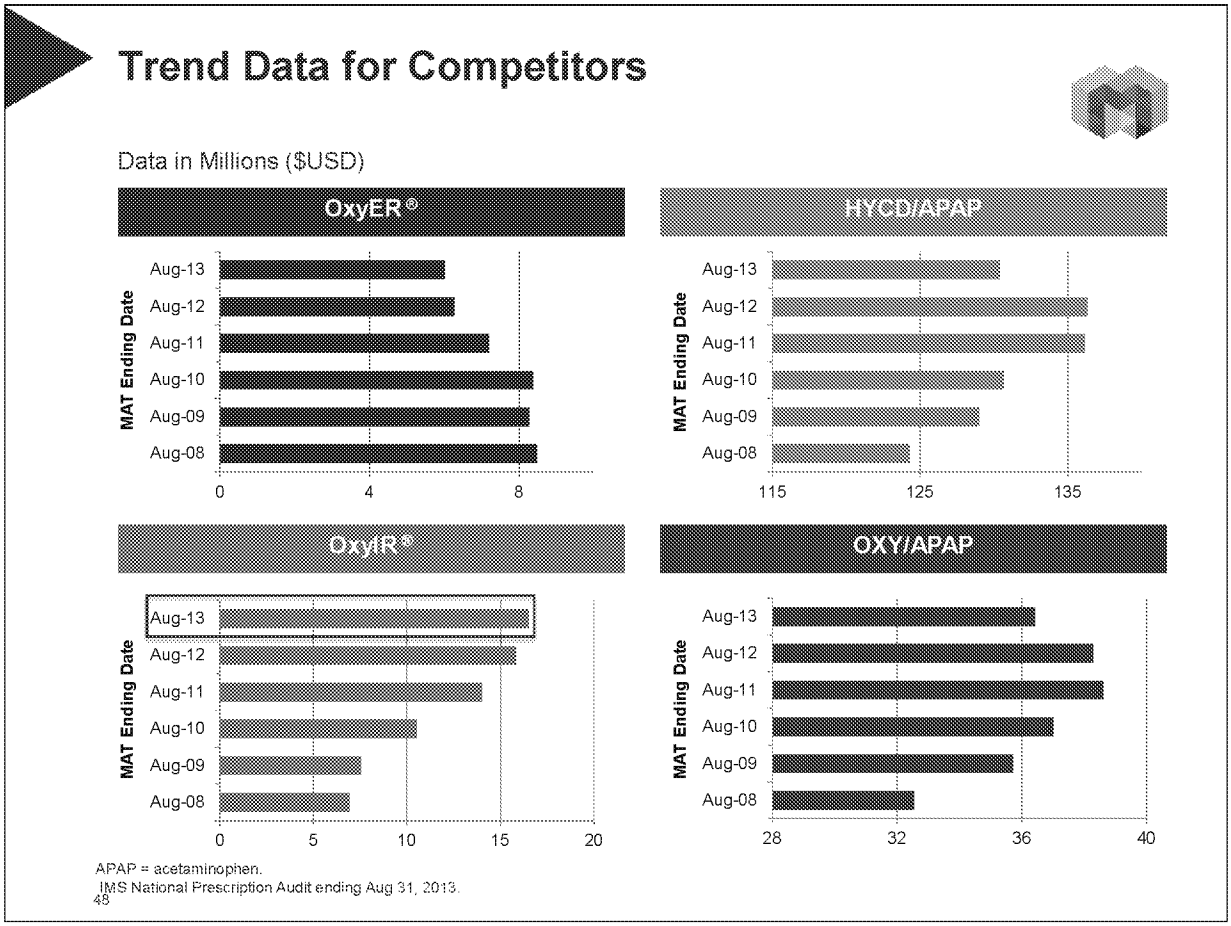
Reference
IMS LRx Xponent, July 2012 to June 2013.



Looking at a snapshot of acute pain prescriptions from July 2012 through June 2013, hydrocodone and hydrocodone combination products make up a vast majority of the acute pain market.

References

1. IMS LRx Xponent, July 2012 to June 2013.



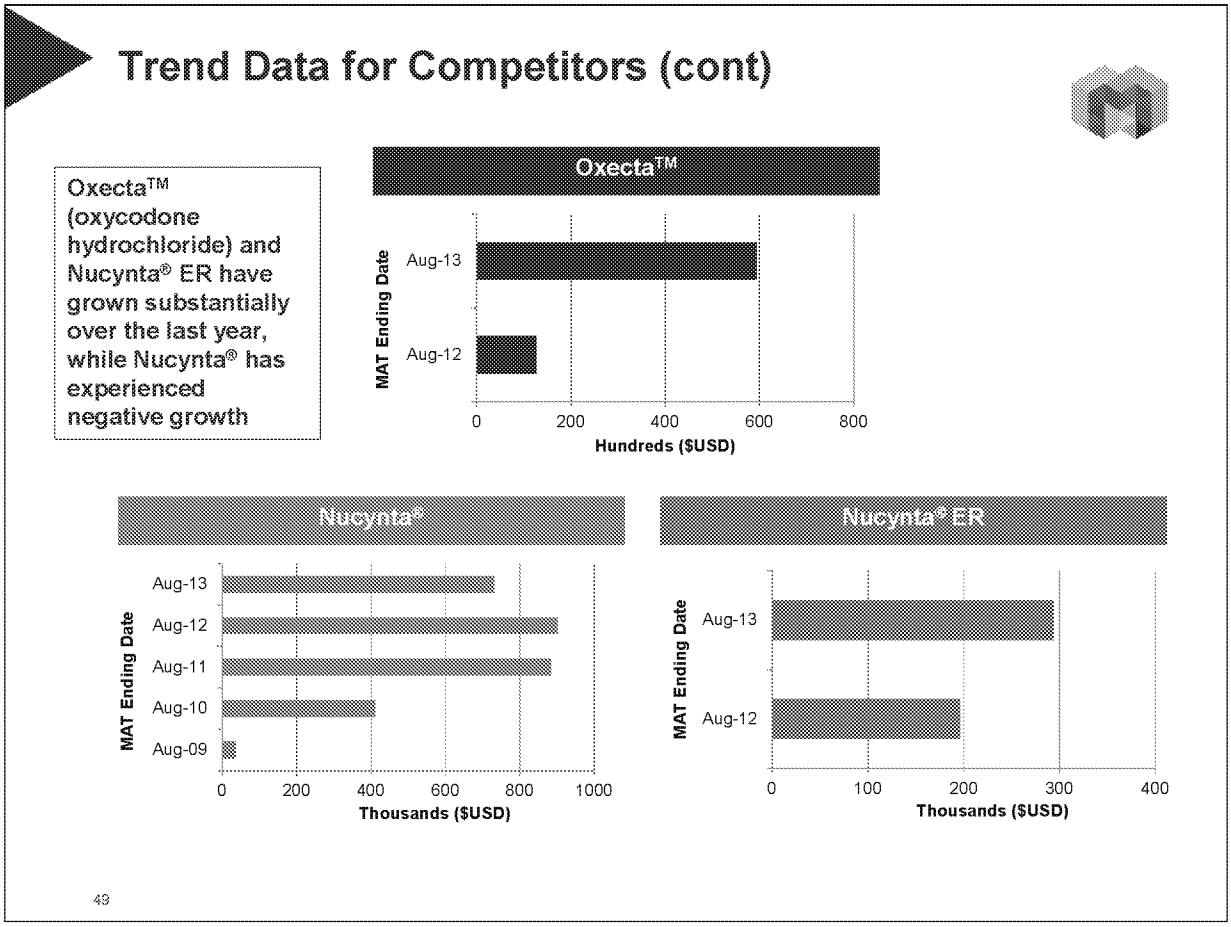
If we look at prescription tend data in millions of US dollars shown by competitor, of these products, OxyIR is the only one that has undergone growth (4.3%) over the past 12 months (see below).

HYCD/APAPOXY EROXY IROXY/APAP
MAT ending Aug-093.8%-2.3%8.9%9.8%
MAT ending Aug-101.3%1.1%39.5%3.6%
MAT ending Aug-114.2%-14.1%33.3%4.3%
MAT ending Aug-120.1%-12.9%13.0%-0.8%
MAT ending Aug-13-4.4%-4.0%4.3%-4.9%

MAT = moving annual total…MAT ending Aug means it includes September through August data.

References

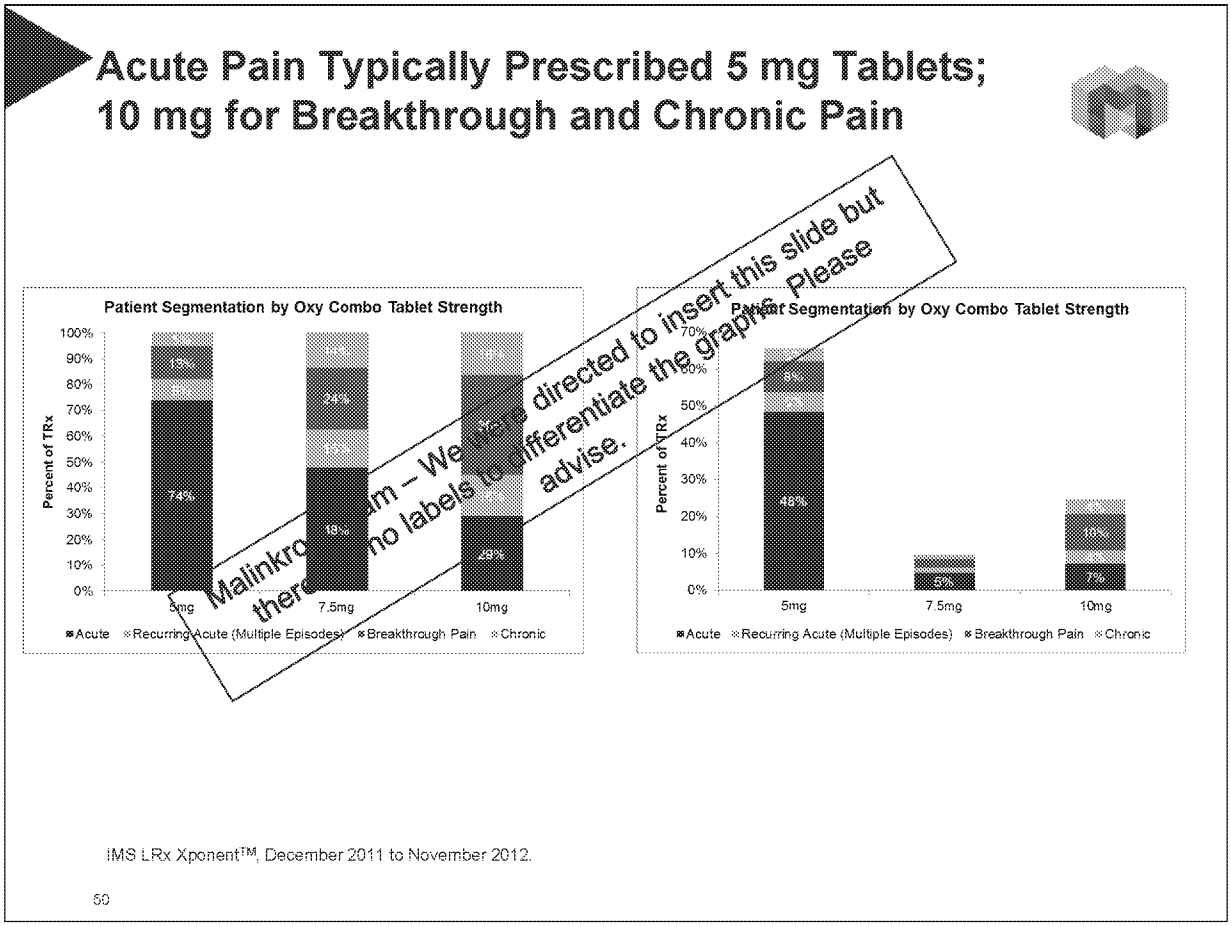
1. IMS National Prescription Audit ending Aug 31, 2013.



Looking at trend data for OxectaTM, Nucynta® ER, and Nucynta®, the 2 products OxectaTM and Nucynta® ER have experienced substantial growth while Nucynta® has experienced negative growth.

References

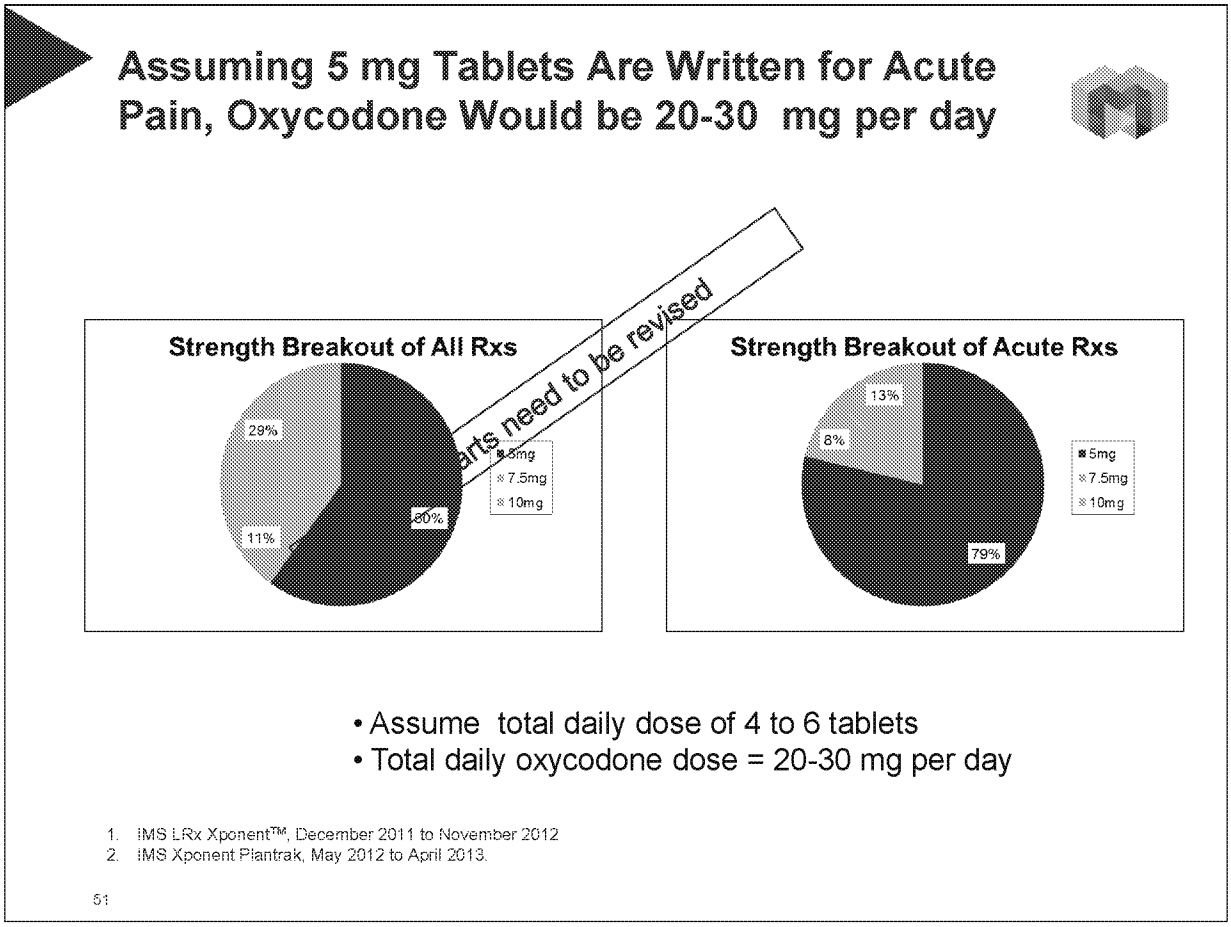
1. IMS National Prescription Audit ending Aug 31, 2013.



As depicted above, the 5 mg tablets are typically prescribed to patients with acute pain, while the 10 mg tablets are often used for patients with chronic and breakthrough pain.

References

IMS LRx XponentTM, December 2011 to November 2012.



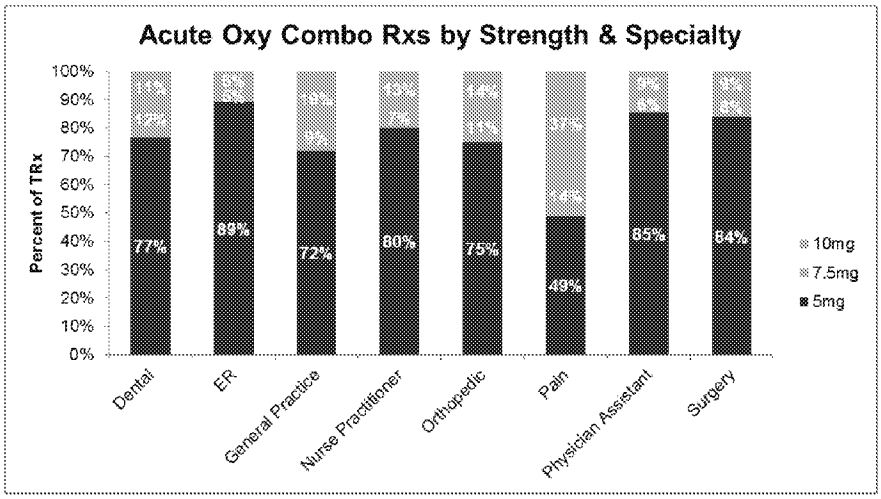
Assuming the 5 mg tablets are typically prescribed for acute pain, and 4 to 6 tablets per day are taken, then the daily dosage of oxycodone would be 20-30 mg per day.

References

1. IMS LRx XponentTM, December 2011 to November 2012.
2. IMS Xponent Plantrak, May 2012 to April 2013.

Notable Differences in Strength Utilization Exist Across Specialties

- ER, PAs, and surgeons are most likely to prescribe 5 mg tablet



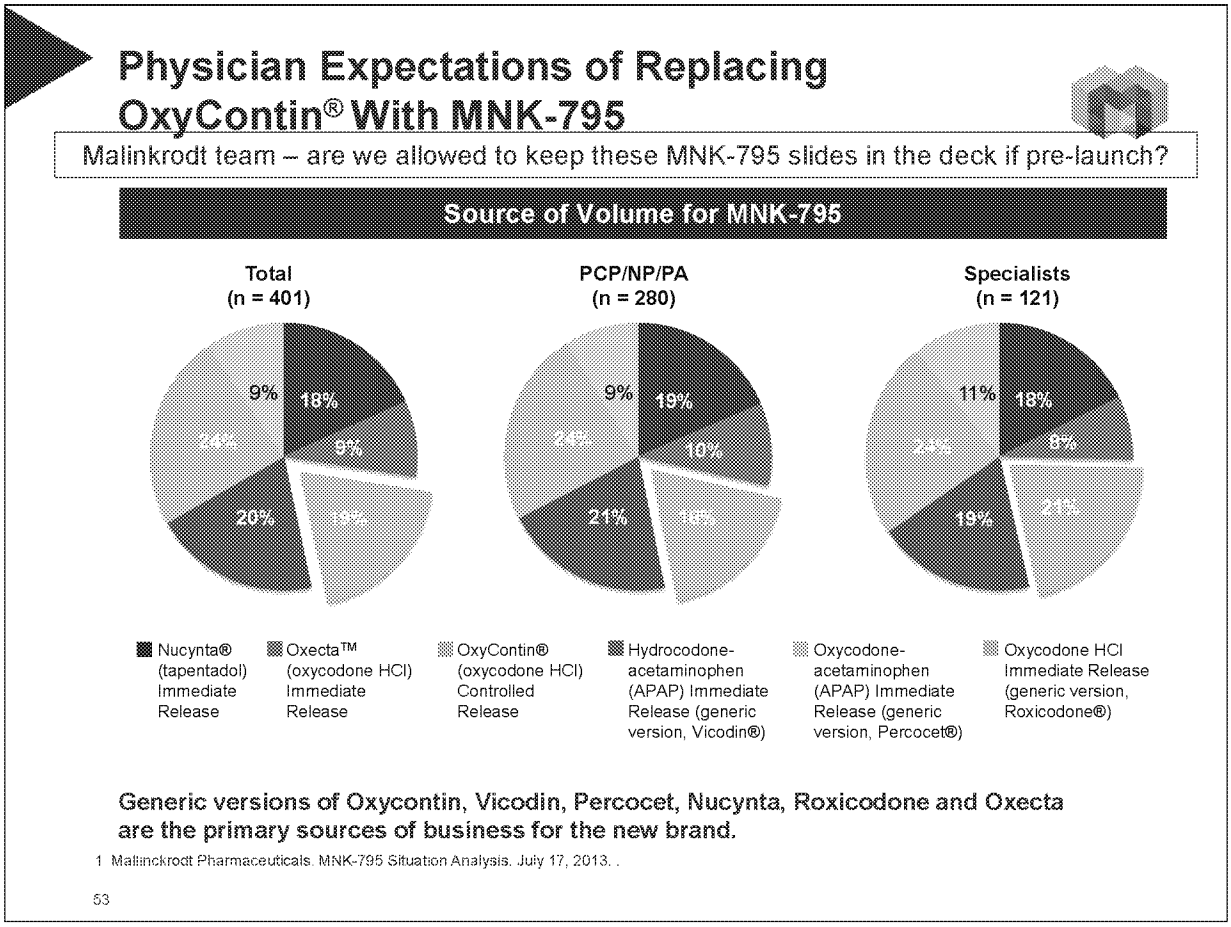
IMS LRx Xponent™, December 2011 to November 2012.

52

Different specialties tend to prescribe different strengths. Notable differences in strength utilization exist across specialties. ER, PAs and surgeons are the most likely to prescribe the 5 mg tablet.

References

IMS LRx XponentTM, December 2011 to November 2012.



To determine potential market sources, physicians were asked how they would distribute their prescriptions across existing products with and without MNK-795 included in the marketplace. This slide shows the proportion of reallocation from existing products to MNK-795.

Overall, 19% of physicians would replace a portion of their OxyContin prescriptions with scripts for MNK-795. Slightly more specialists would do so than primary care physicians (21% vs 18%, respectively).

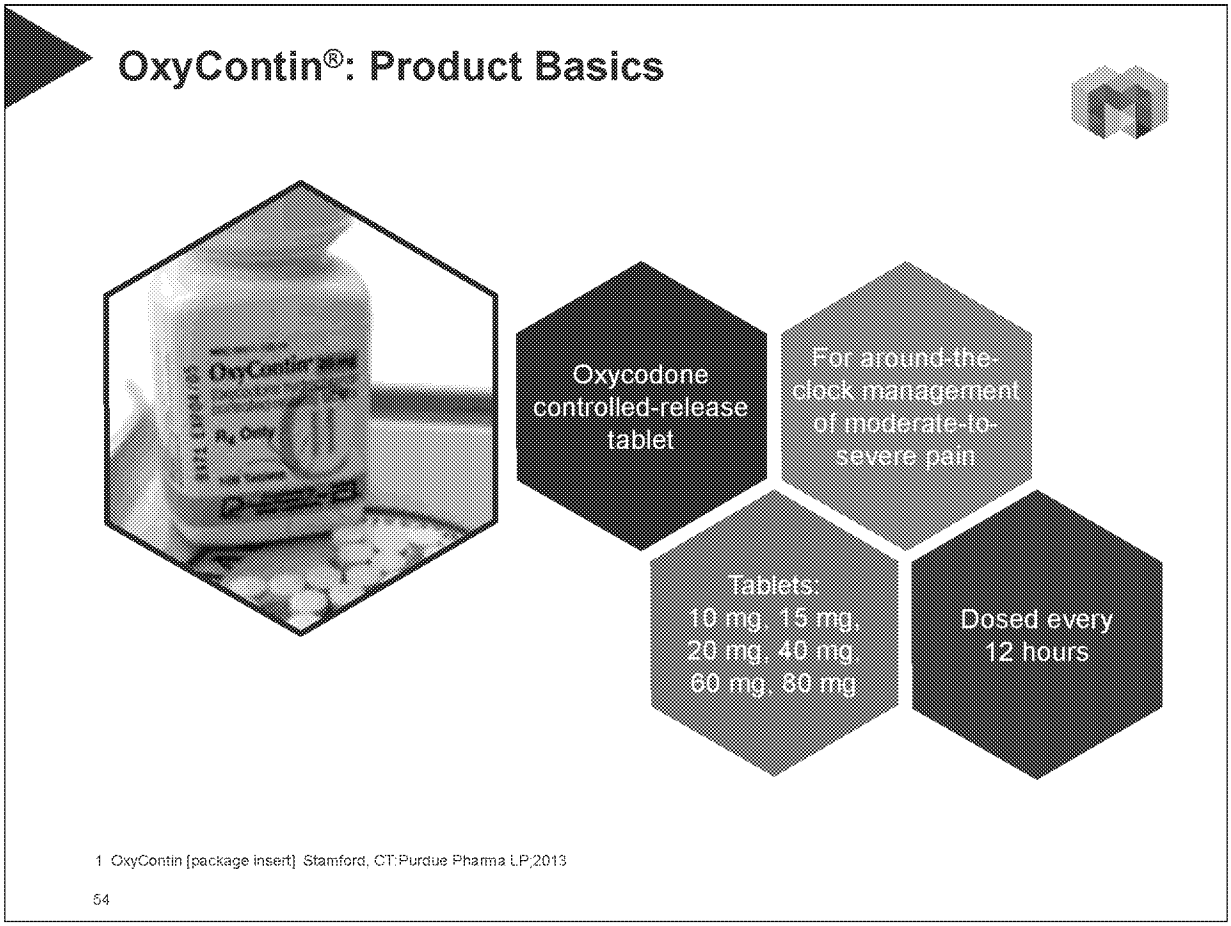
References

1. Mallinckrodt Pharmaceuticals. MNK-795 Situation Analysis. July 17, 2013.

TINA:

Use this slide to set up the competitive landscape, before launching into each of the individual products.

Situation analysis slide 83
Mallinckrodt Pharmaceuticals, data on file.



The OxyContin® label is specific that it is not to be used for acute pain or for postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or unless the postoperative pain is expected to be moderate to severe and persisting for an extended period of time. The label precludes PRN use. With new labeling requirements, the label can no longer claim an indication for moderate pain.

References

1. OxyContin [package insert]. Stamford, CT:Purdue Pharma LP;2013.

Example image:

http://hereandnow.wbur.org/2012/03/28/oxycontin-canada-ontario

OxyContin PI p1 A

Sept 10 UCM p 8A

OxyContin PI p1 B

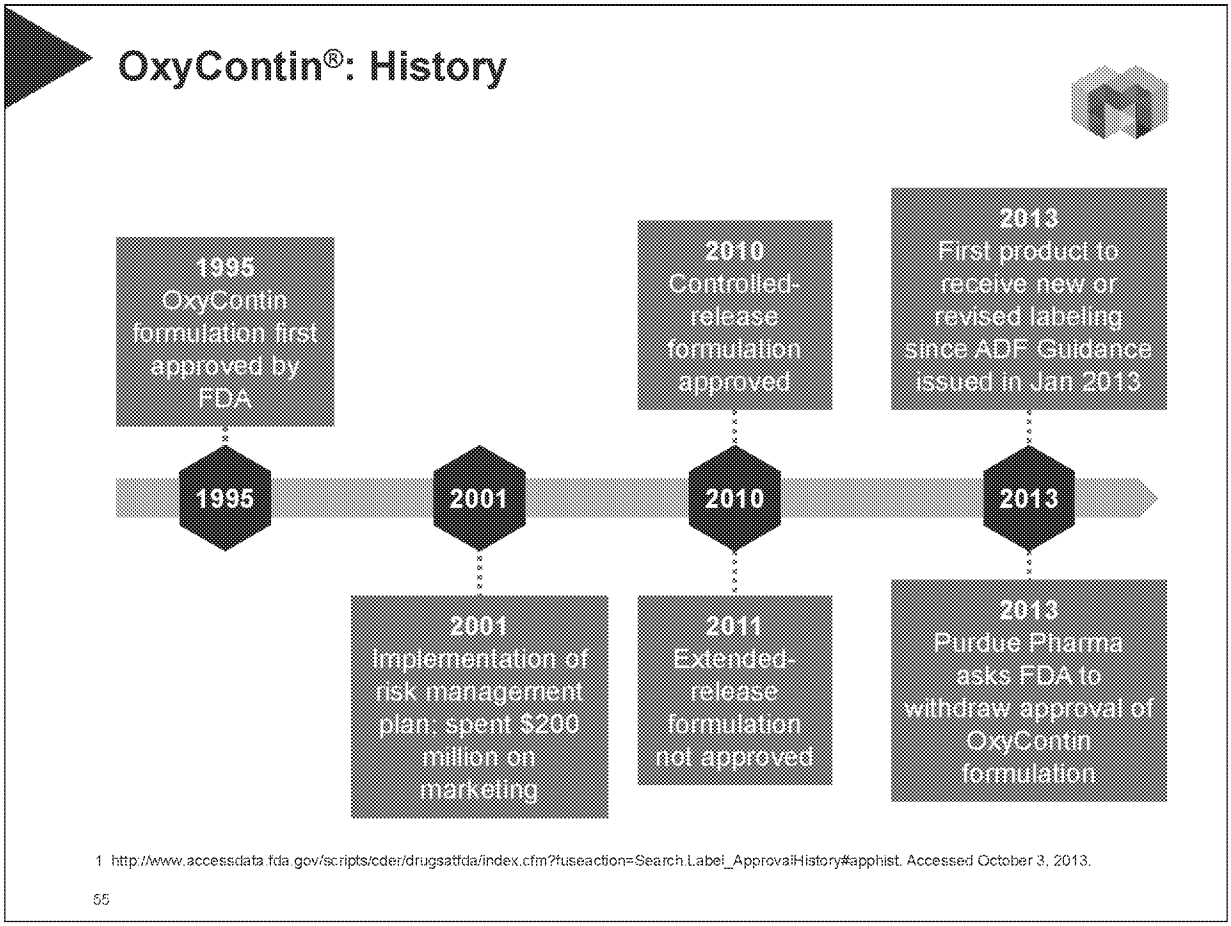
OxyContin PI p1 C

Oxycontin PI p5A

OxyContin[package insert]. Stamford, CT:Purdue Pharma LP;2013.

Food and Drug Administration.

http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf. Accessed September 11, 2013.



In response to abuse of OxyContin among recreational drug users, Purdue worked with the FDA to develop a risk management plan. Implemented in 2001, the plan included education and outreach, labeling changes, surveillance and intervention. Generics were introduced and phased out of the market. Oxycontin was the first to receive new/revised labeling since the January 2013 issuance of ADF guidance.

According to claims in the latest 2013 Oxycontin PI, in vitro data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult and that are also expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes, as well as by the oral route is still possible. Also according to the label, OxyContin can be abused and is subject to misuse, addiction and criminal diversion.

References

Label and approval history:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed October 3, 2013.
OxyContin [package insert]. Stamford, CT:Purdue Pharma LP;2013.

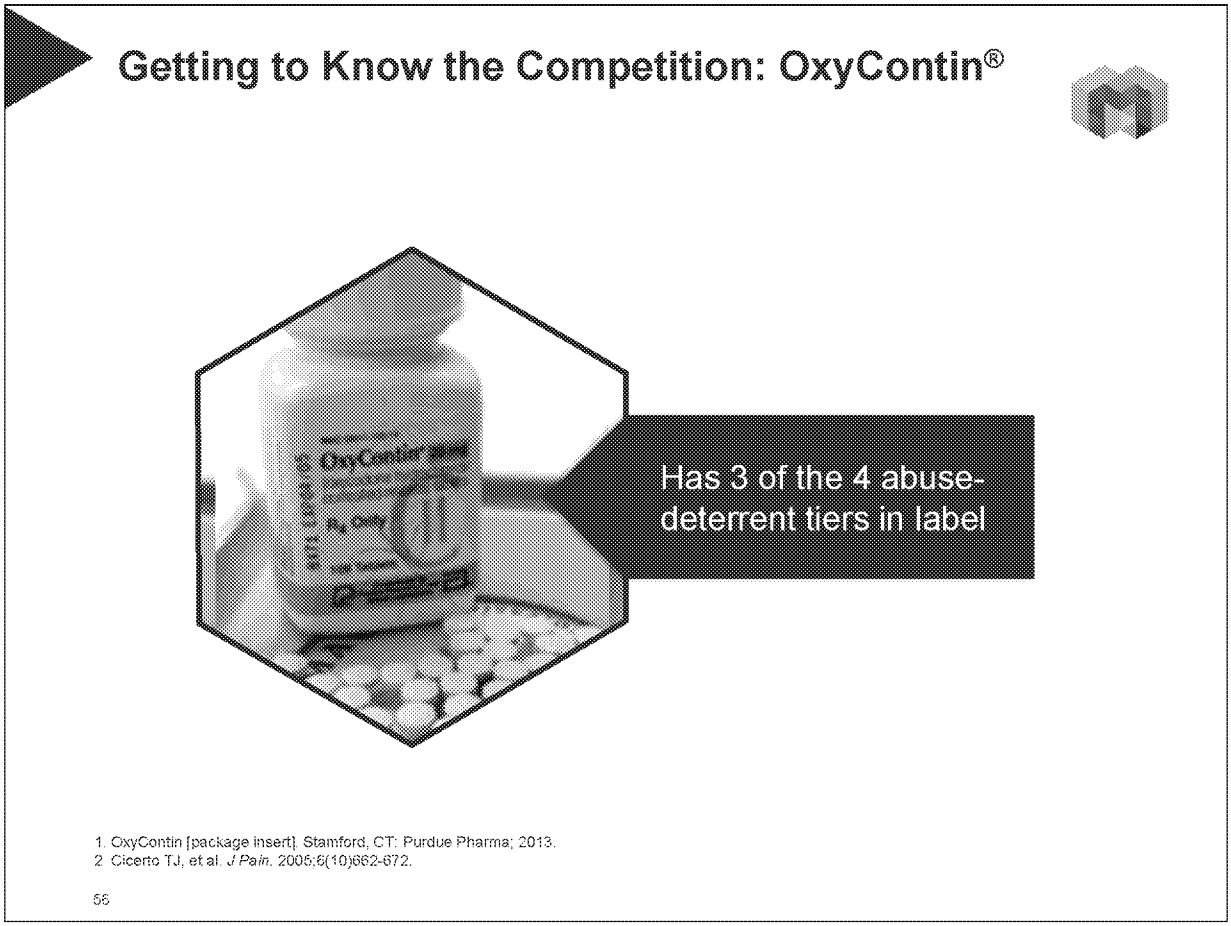
Introduction of generics
Phase-out of generics from the market
January Include key dates from this year's label update to include claims in accordance with FDA Guidance on ADFs – Section 9.2 of the PI

TINA:

Please include revised label as of 2013 – first product to receive new or revised labeling since January 2013 ADF Guidance Issuance

FDA History of oxycontin, slides 11-13

Abuse-deterrent deck slide 18



OxyContin extended-release label contains abuse-deterrent studies consistent with FDA categories 1-3. Once post-marketing data are available, this will be the first product to obtain revised labeling following the introduction of the FDA Guidance on abuse deterrent formulations.

OxyContin bridges the prescribing gap between acute and chronic pain, but is not indicated for acute pain, and it has a stigma of abuse.

Reference

1. OxyContin [package insert]. Stamford, CT: Purdue Pharma; 2013.
2. Cicerto TN, Inciardi JA, Munõz A. Trends in abue of oxycontin and other opioid analgesics in the United States: 2002-2004. J Pain. 2005;6(10):662-672.

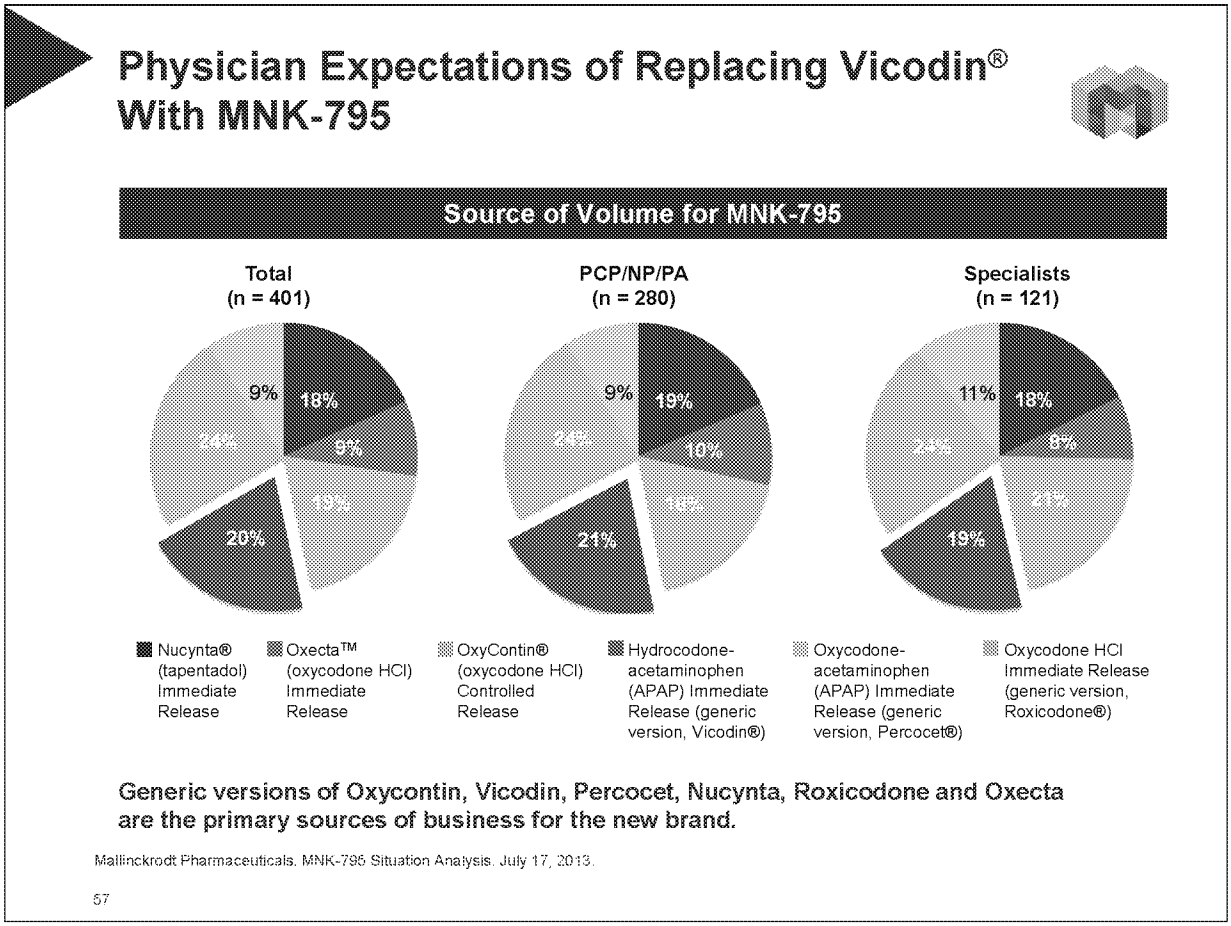
Example image:

http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html

OxyContin[package insert]. Stamford, CT:Purdue Pharma LP;2013.

OxyContin PI p. 16 A, B; p. 17A

OxyContin PI p. 16 A, B; p. 17A



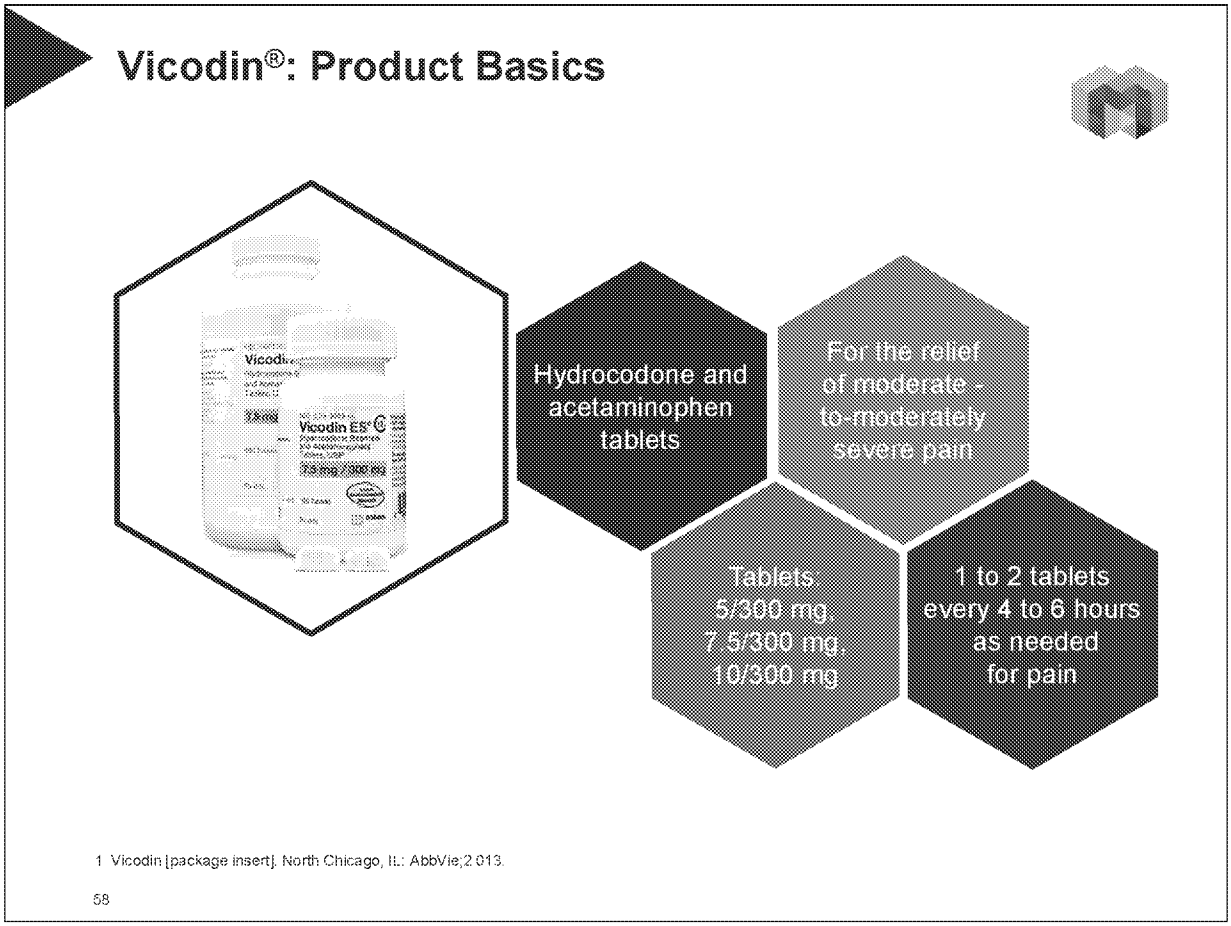
Overall, 20% of physicians would replace a portion of their Vicodin® (hydrocodone-acetaminophen) prescriptions with scripts for MNK-795. There was not much difference between specialists and primary care physicians (19% vs 21%, respectively).

Reference

Mallinckrodt Pharmaceuticals. MNK-795 Situation Analysis. July 17, 2013.

Situation analysis slide 83

Mallinckrodt Pharmaceuticals, data on file.



Currently, Vicodin® is indicated for the relief of moderate or moderately severe pain, but the indication does not specify acute or chronic pain. Dosing for 3 strengths is 1 or 2 tablets every 4 to 6 hours. The maximum number of tablets is 8 daily for the 5/300 mg tablets and 6 daily for either of the higher doses.

Reference

Vicodin [package insert]. North Chicago, IL: AbbVie; 2013.

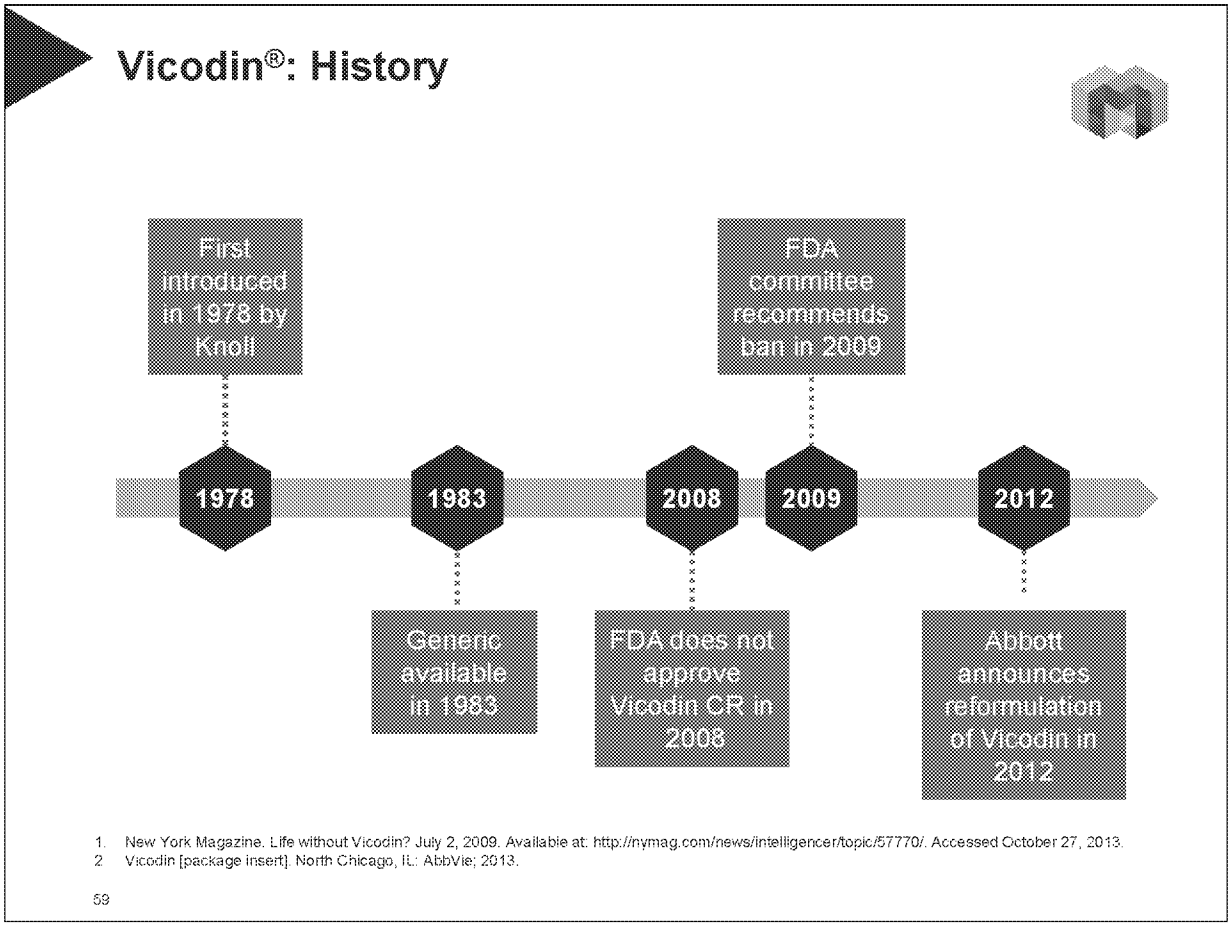
Example image:

http://www.vicodin.com/hcp/dosage.cfm

Vicodin PI p 4 A

Vicodin PI p1 A

Vicodin PI p 11 A



Knoll first introduced Vicodin® in 1978, and its generic formulation became available in 1983. In 2006, Americans were written 130 million prescriptions for hydrocodone-containing products. In 2008, Abbott planned to market a controlled-release Vicodin product; however, the product did not receive FDA approval, and, within a few months, Abbott laid off approximately 200 sales representatives designated to sell the product. A federal advisory panel voted on June 30, 2009, to recommend that the FDA ban Vicodin.1 The product has since been reformulated in keeping with FDA recommendations and is available as hydrocodone/acetaminophen 5/300 mg, 7.5/300 mg and 10/300 mg.2

References

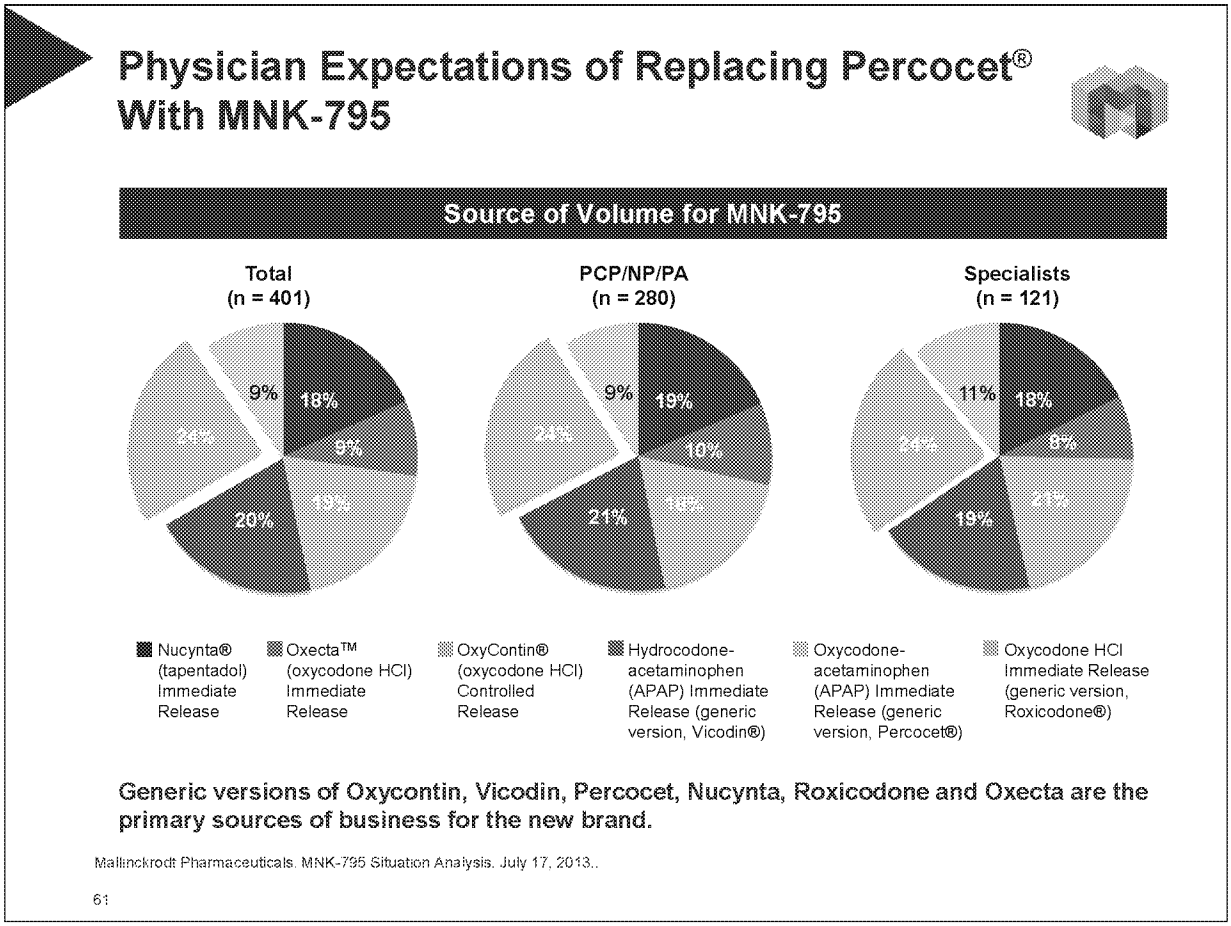
New York Magazine. Life without Vicodin? July 2, 2009. Available at: http://nymag.com/news/intelligencer/topic/57770/. Accessed October 27, 2013.
Vicodin [package insert]. North Chicago, IL: AbbVie; 2013.

COMMENTS:
2008: Vicodin CR denied by FDA
Include release of reformulation by Abbott

Collectively, Vicodin® (hydrocodone plus acetaminophen) and its numerous generic versions continue to be the most widely prescribed medication in the United States.1 Abbvie, Inc., the manufacturer of Vicodin, released a formulation containing 300 mg of acetaminophen in advance of the FDA deadline for reformulation, which is January 2014.2 Two states have reclassified Vicodin as a schedule II drug.3,4

References

Manchikanti L, Helm S II, Fellow B, et al. Opioid epidemic in the United States. Pain Physician 2012;15(3 Suppl):ES9-ES38.
Vicodin Web site. Available at: http://www.vicodin.com/hcp/?cid=ppc_ppd_vcdn_ggl_ppc_0616. Accessed September 12, 2013.
Oklahoma Department of Health. Available at: http://www.ok.gov/OSBP/Announcements/. Accessed September 10, 2013
Department of Health of the State of NY. Available at:
http://www.health.ny.gov/professionals/narcotic/laws_and_regulations/part_c-chapter_447-laws_of_2012-faq.htm. Accessed September 10, 2013.
Example image:
http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html
Manchikanti p ES23A
Manchikanti p ES23A
2/Vicodin web site p 1A



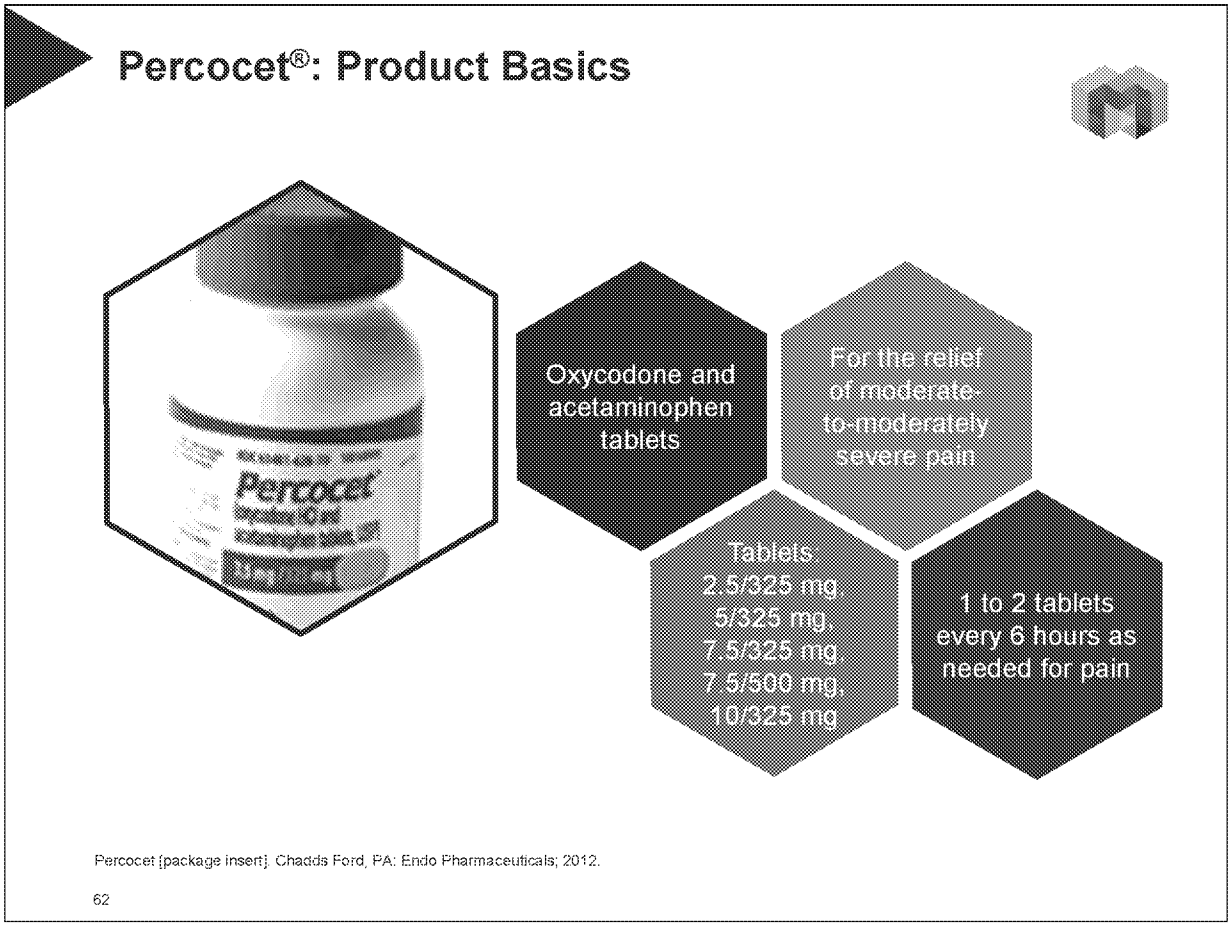
Overall, 24% of physicians would replace a portion of their oxycontin-acetaminophen IR prescriptions with scripts for MNK-795. There was no difference between specialists and primary care physicians (both 24%).

Reference

Mallinckrodt Pharmaceuticals. MNK-795 Situation Analysis. July 17, 2013.

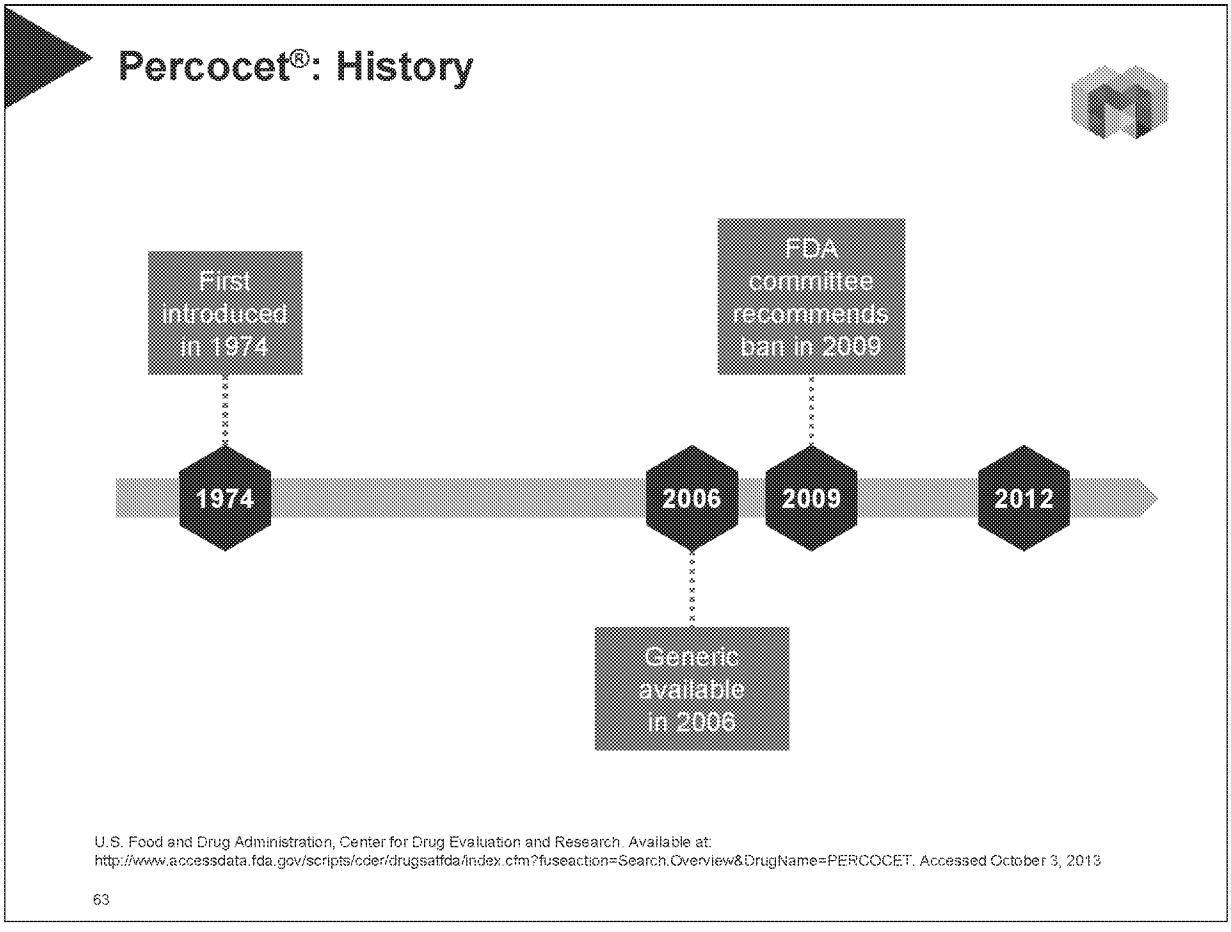
Situation analysis slide 83

Mallinckrodt Pharmaceuticals, data on file.



Currently, Percocet®, like Vicodin, is indicated for relief of moderate-to-moderately severe pain, without specifying whether it is for use in acute or chronic pain. Although most tablets meet the FDA recommended dose of acetaminophen (≤325 mg/tablet), the highest available dose is 500 mg/tablet.

Reference
Percocet [package insert]. Chadds Ford, PA: Endo Pharmaceuticals; 2012.
Example image:
http://drugsnow.org/percocet-withdrawal-symptoms/
Percocet PI p. 1A
Percocet PI p. 2A
Percocet PI p. 4A
Percocet PI p. 18A
Percocet [package insert]. Chadds Ford, PA: Endo Pharmaceuticals;2012.
Percocet PI p. 4A
Percocet PI p. 18A

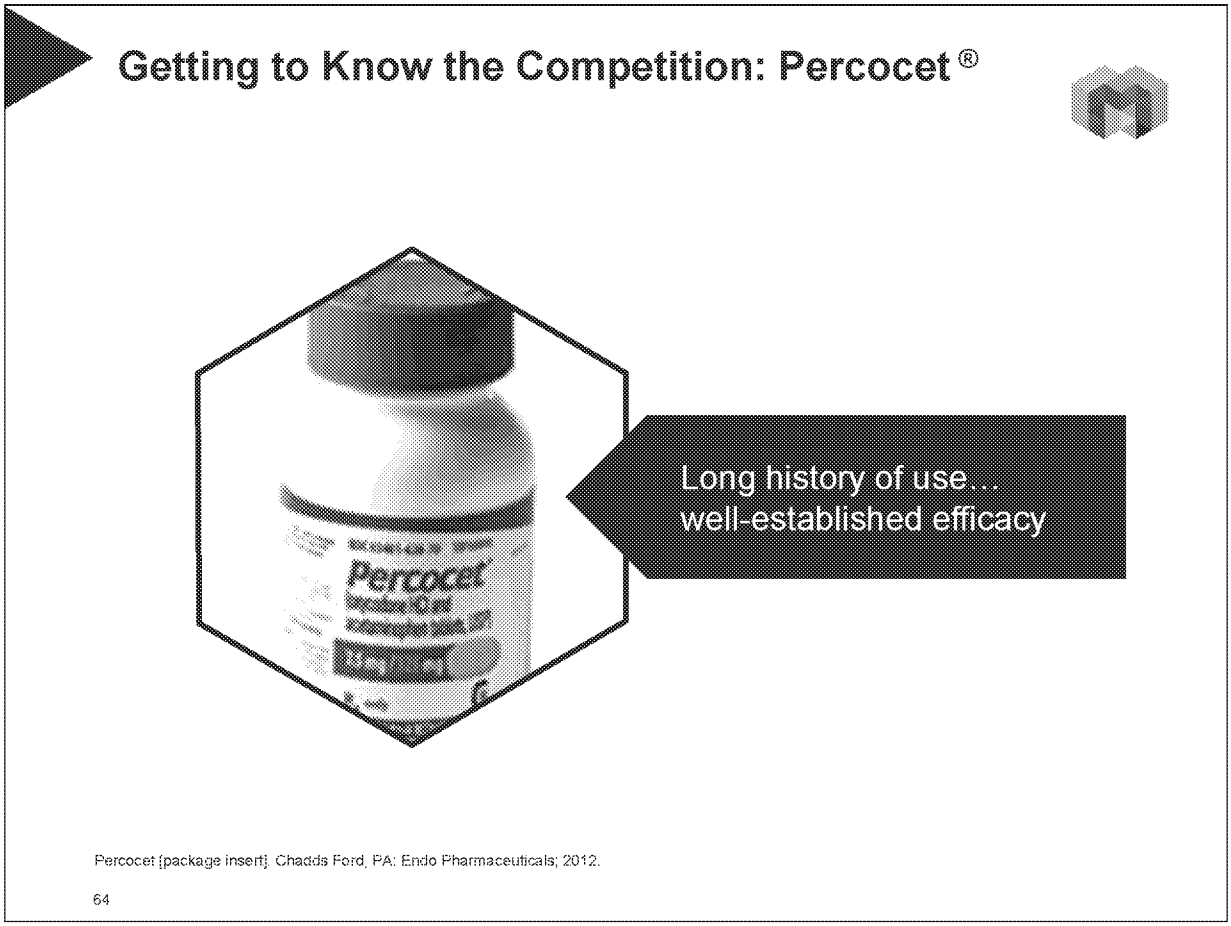


The FDA initially approved Percocet® in 1976 as a Vintage Pharms LLC product under application ANDA 085106.1 Then in March of 2006 Endo began making Percocet in 6 different dosages. Endo was created as a result of a management buyout by DuPont Merck management in 1997. In June of 2009, an FDA advisory panel recommended that Percocet sales be limited due to its contributions to acetaminophen-related US deaths every year secondary to hepatic injury.2

References

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=PERCOCET. Accessed October 3, 2013.

Los Angeles Times. FDA panel calls for restrictions on Tylenol, Vicodin, Percocet. July 1, 2009. Available at: http://articles.latimes.com/2009/jul/01/nation/na-tylenol1. Accessed October 17, 2013. [Ref: LA Times FDA panel calls for restrictions on Tylenol]

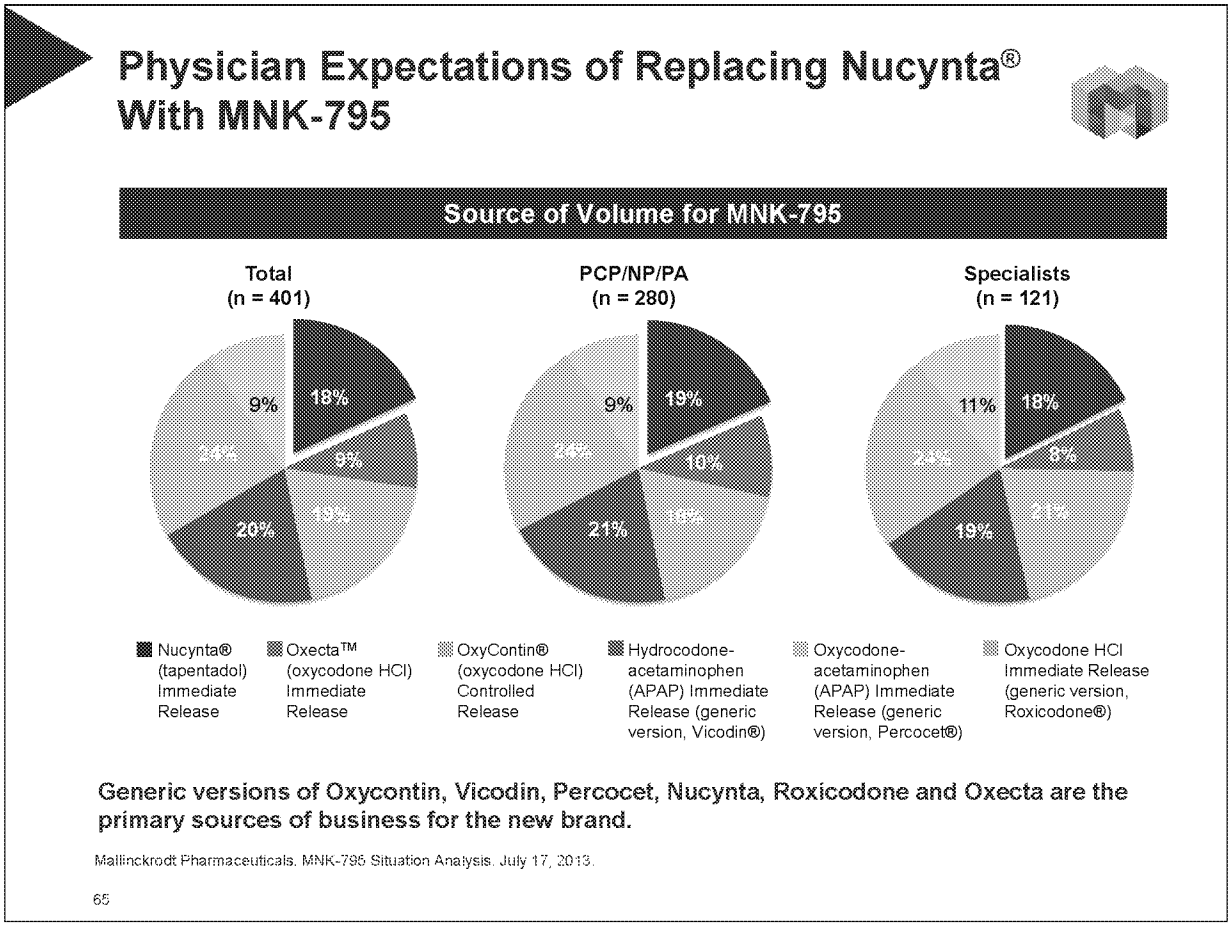


Available since the 1990s, Percocet® (oxycodone/APAP combination) immediate-release formulation has longstanding name recognition and its efficacy is well established. Along with the generic version, Percocet is the Number 2 opioid prescribed.

References

Percocet [package insert]. Chadds Ford, PA: Endo Pharmaceuticals; 2012.
MNK795 Situation Analysis: Market Overview and Market Map. Mallinckrodt Pharmaceuticals; 2013.

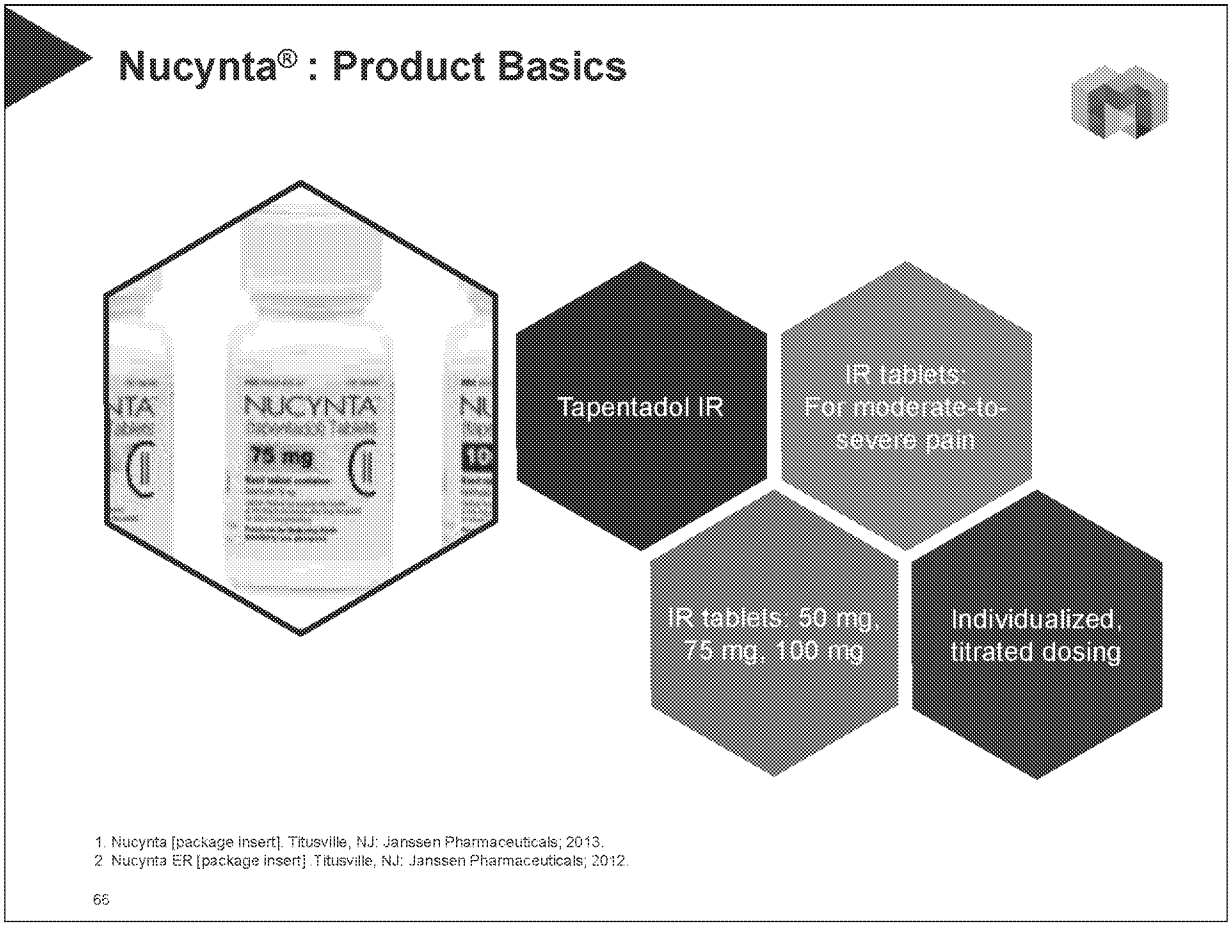
Example image:
http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html
Manchikanti p ES23A



Overall, 18% of physicians would replace a portion of their Nucynta IR prescriptions with scripts for MNK-795. There was essentially no difference between specialists and primary care physicians (19% vs 18%, respectively). Nucynta ER was not included in this market research exercise.

Reference

Mallinckrodt Pharmaceuticals. MNK-795 Situation Analysis. July 17, 2013.
Situation analysis slide 83



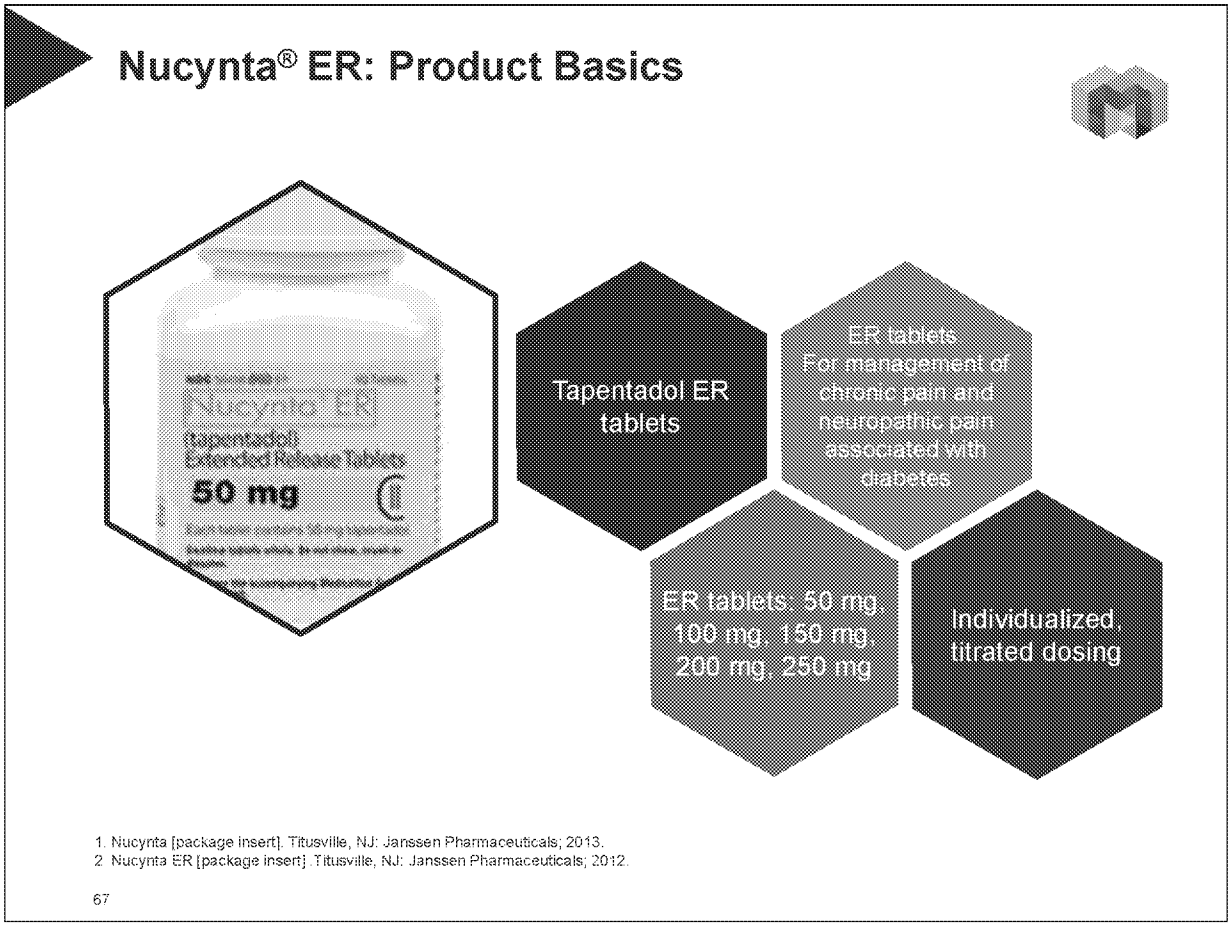
Nucynta® immediate-release tablets were approved in 2008 for treatment of moderate-to-severe pain. Nucynta is indicated for acute pain.

References

Nucynta ER [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2012.
Nucynta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.

Example image:
http://www.empr.com/nucynta-er-approved-for-neuropathic-pain/article/256569/
1/Nucynta p. 1A
2/Nucynta ER p. 1A
1/Nucynta p. 1A
2/Nucynta ER p. 1A
1/Nucynta p. 1B
2/Nucynta ER p. 1B

1/Nucynta p. 1D
2/Nucynta ER p. 3A
1/Nucynta p. 1C
2/Nucynta ER p. 1C
2/Nucynta ER p. 1B



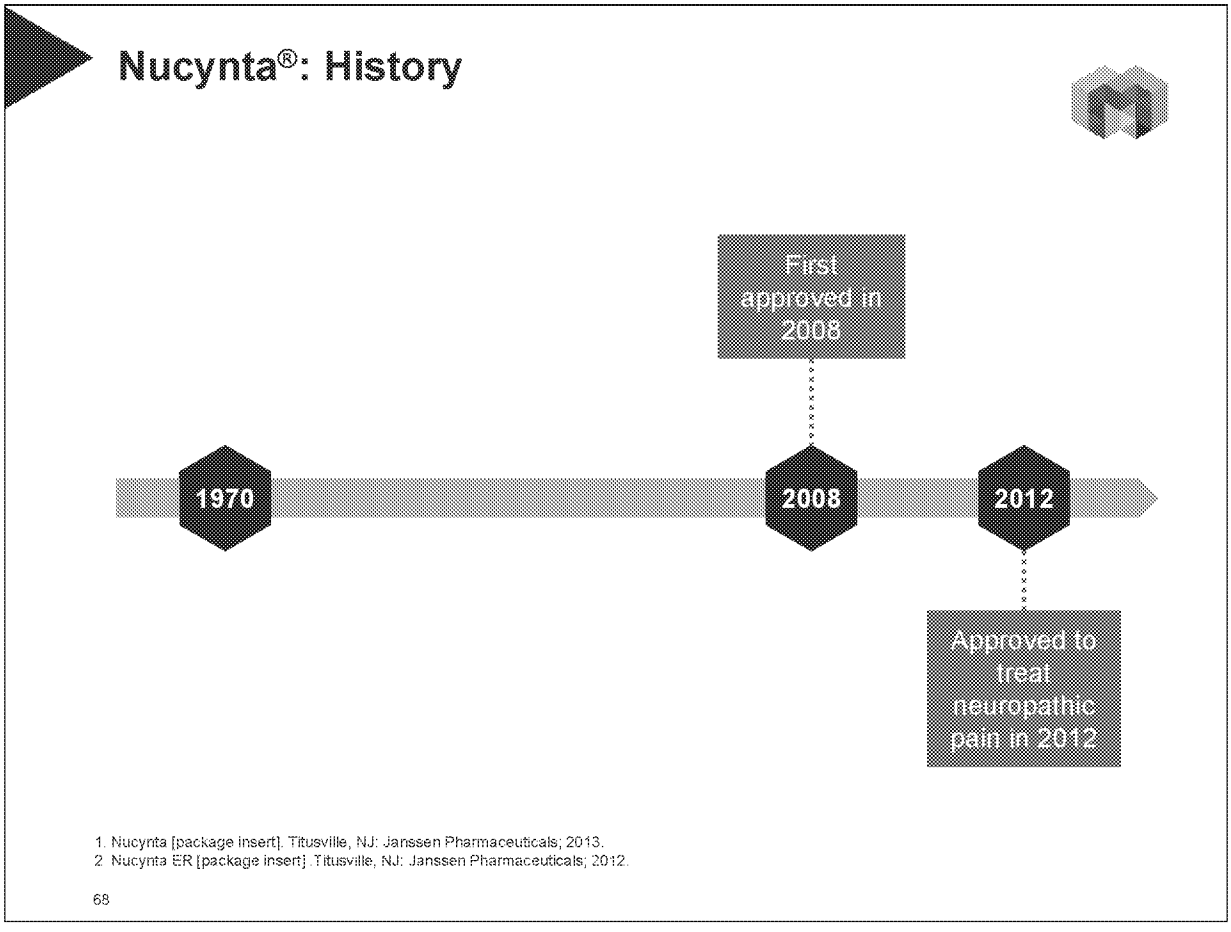
Nucynta® extended-release (ER) tablets were also approved in 2008 for treatment of moderate-to-severe pain. Nucynta ER is also indicated for neuropathic pain associated with diabetic neuropathy. The package insert for the ER formulation specifies that it be used when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The ER formulation is indicated for chronic pain.

References

Nucynta ER [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2012.
Nucynta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.

Example image:
http://www.empr.com/nucynta-er-approved-for-neuropathic-pain/article/256569/
1/Nucynta p. 1A
2/Nucynta ER p. 1A
1/Nucynta p. 1A
2/Nucynta ER p. 1A
1/Nucynta p. 1B
2/Nucynta ER p. 1B

1/Nucynta p. 1D
2/Nucynta ER p. 3A
1/Nucynta p. 1C
2/Nucynta ER p. 1C
2/Nucynta ER p. 1B

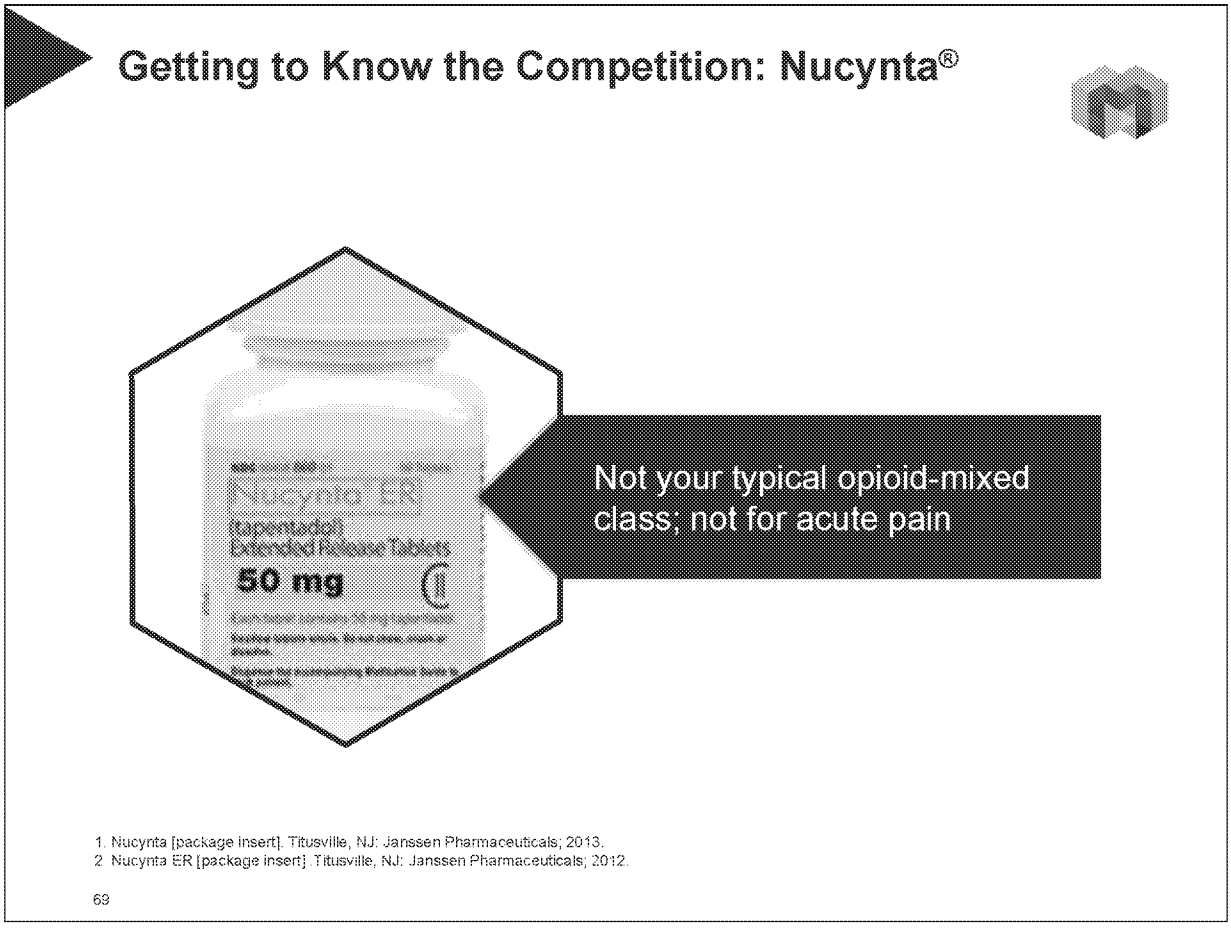


Both formulations were approved in 2008. In 2012, the extended-release formulation received the indication for neuropathic pain associated with diabetic nephropathy.

References

Nucynta ER [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2012.
Nucynta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.

1/Nucynta p. 1A
2/Nucynta ER p. 1A

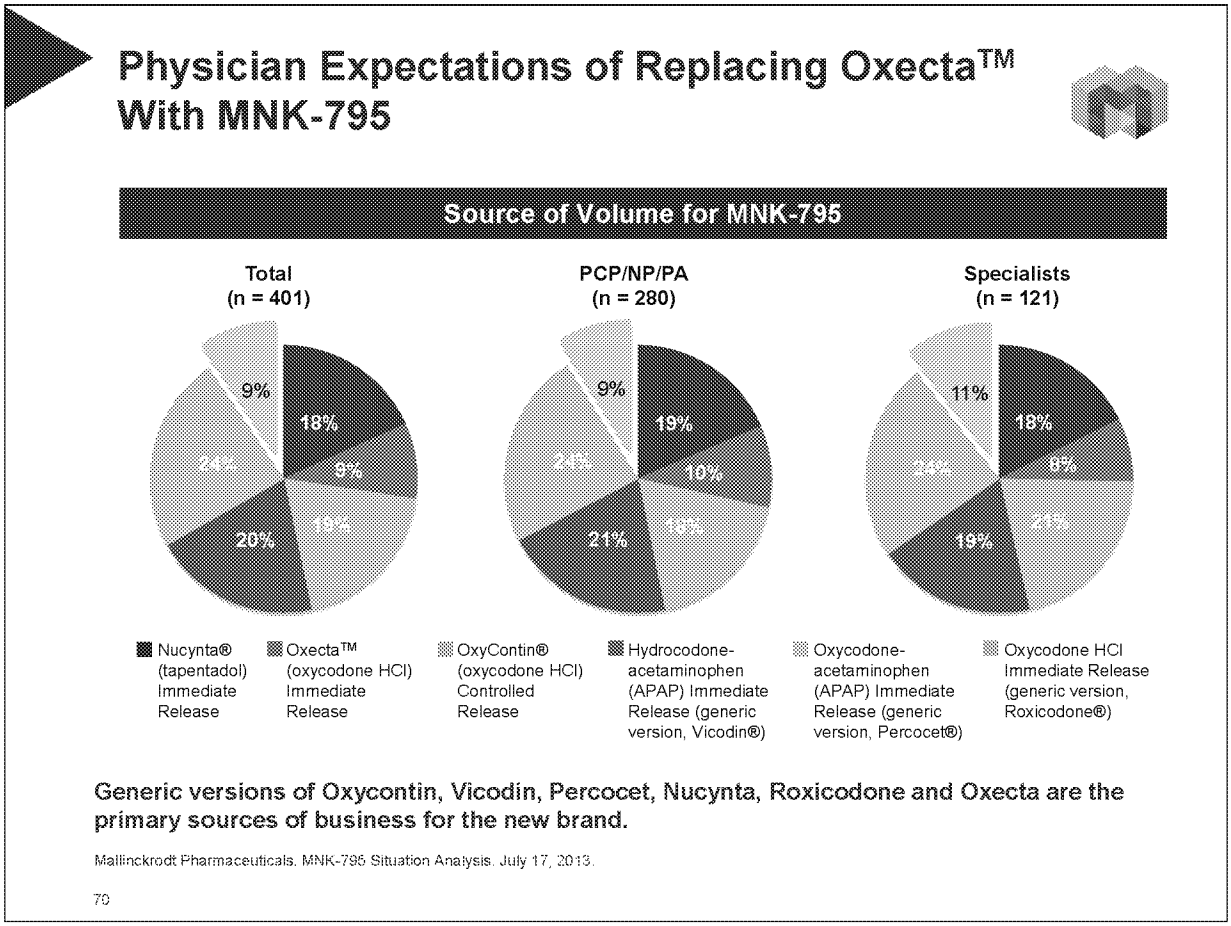


The exact mechanism of action of tapentadol, a centrally acting agent, is unknown. It is thought that its analgesic effects result from a combination of its μ-opioid receptor agonist activity and norepinephrine reuptake inhibition.1

References

Nucynta ER [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2012.
Nucynta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.

Stigma of availability, low stigma of abuse
Marketed as “more tolerable”
Example image:
http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html
Nucynta PI p. 18A
Nucynta PI p.1 -B

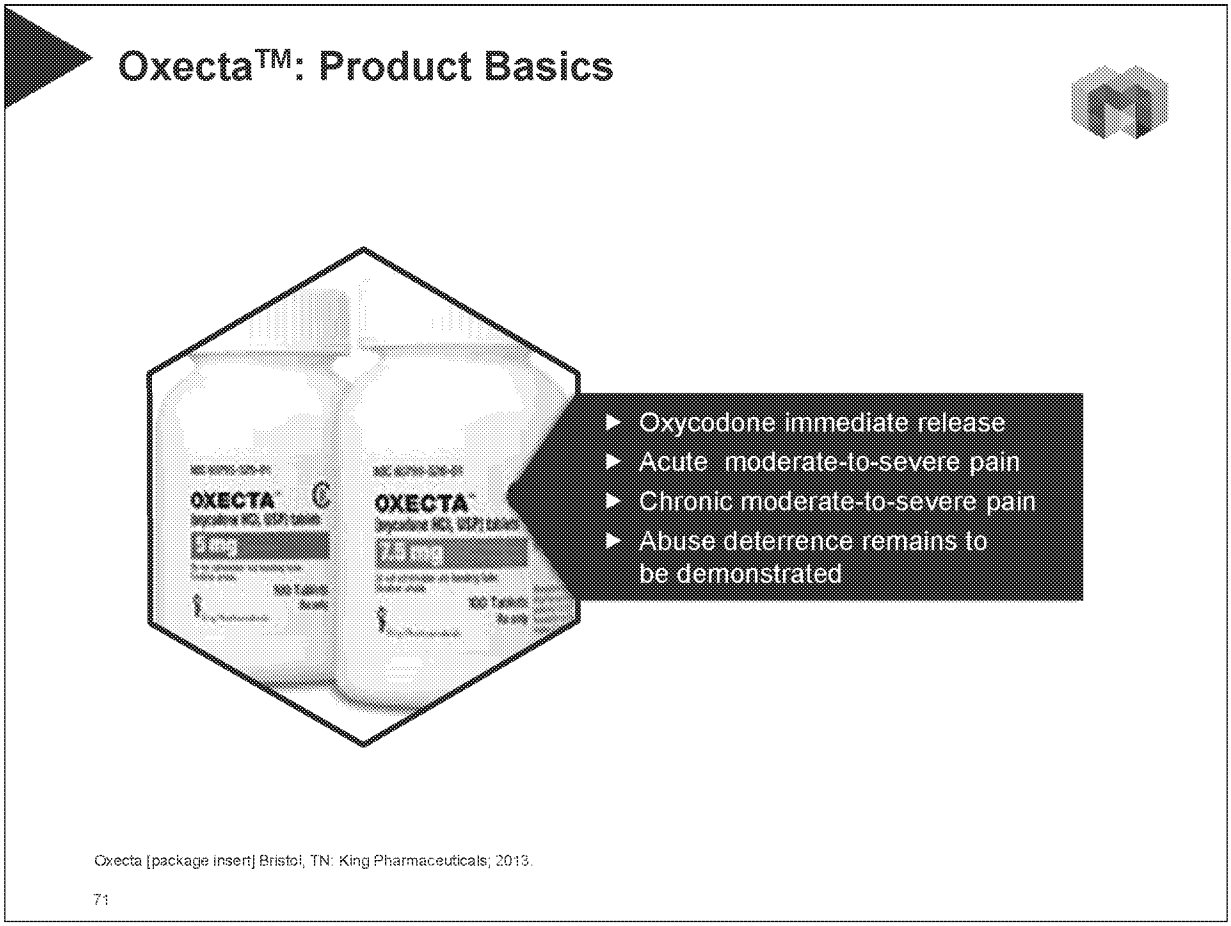


Overall, 9% of physicians would replace a portion of their Oxecta prescriptions with scripts for MNK-795. There was a slight difference between specialists and primary care physicians (8% vs 10%, respectively).

Reference

Mallinckrodt Pharmaceuticals. MNK-795 Situation Analysis. July 17, 2013.

Situation analysis slide 83



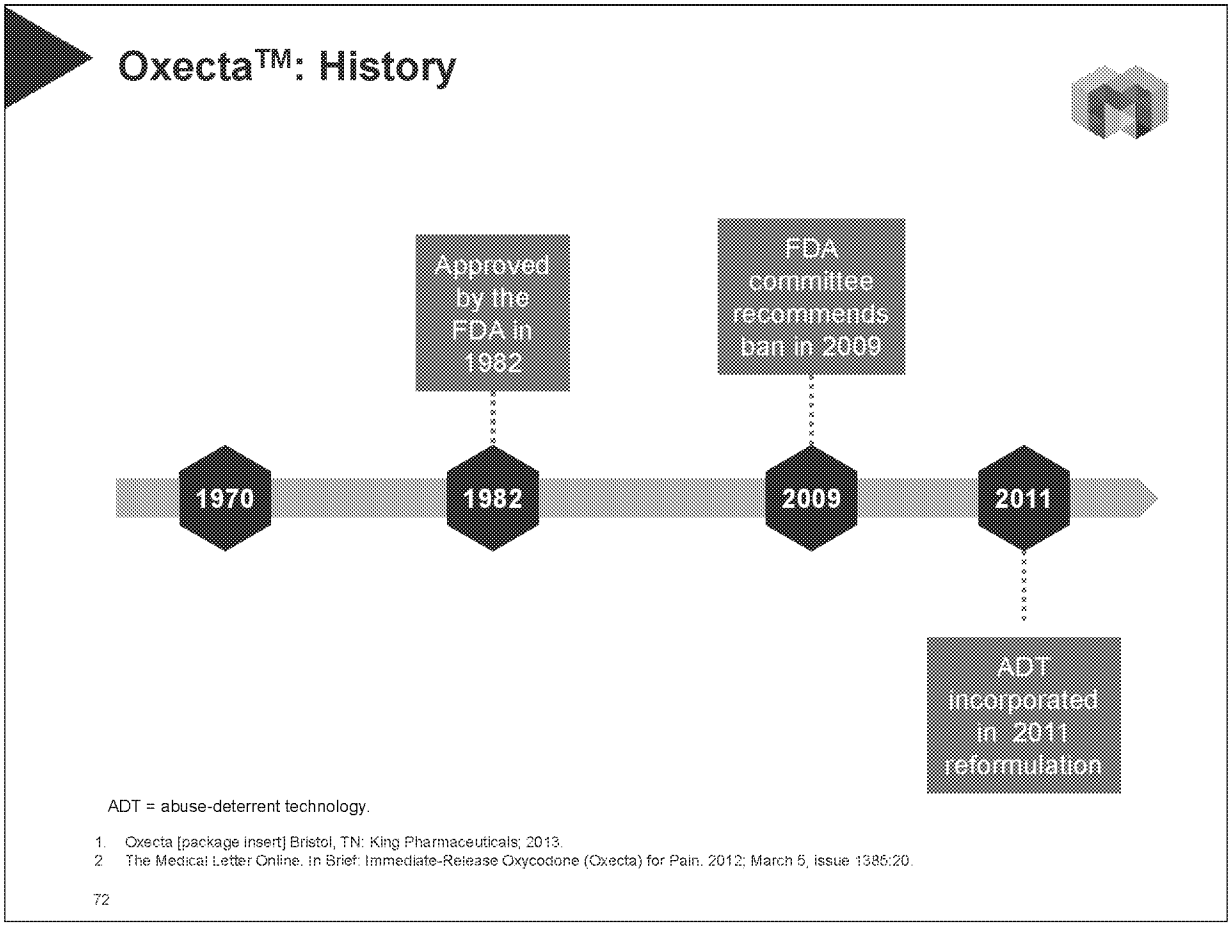
An immediate-release oxycodone product, the abuse deterrence characteristics of Oxecta are achieved through the addition of sodium lauryl sulfate, which makes sniffing the crushed form unpleasant, and attempts to liquify it result in a gel that is difficult to inject.1

Oxecta should not be administered via nasogastric, gastric or other feeding tubes because it may cause obstruction of feeding tubes.2

References

OPTUMRx RxNews — Drug Approvals. OxectaTM (oxycodone) — New Drug Approval. June 20, 2100. Available at: https://www.optumrx.com/RxsolHcpWeb/cmsContent.do?pageUrl=/HCP/RxNews/DrugApprovals/2011&pageName=07012011Oxecta&disclaimer=RxNewsDisclaimer. Accessed October 17, 2013.
Oxecta (oxycodone HCl, USP) [package insert] Bristol, TN: King Pharmaceuticals; 2013.

Example image:
http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html

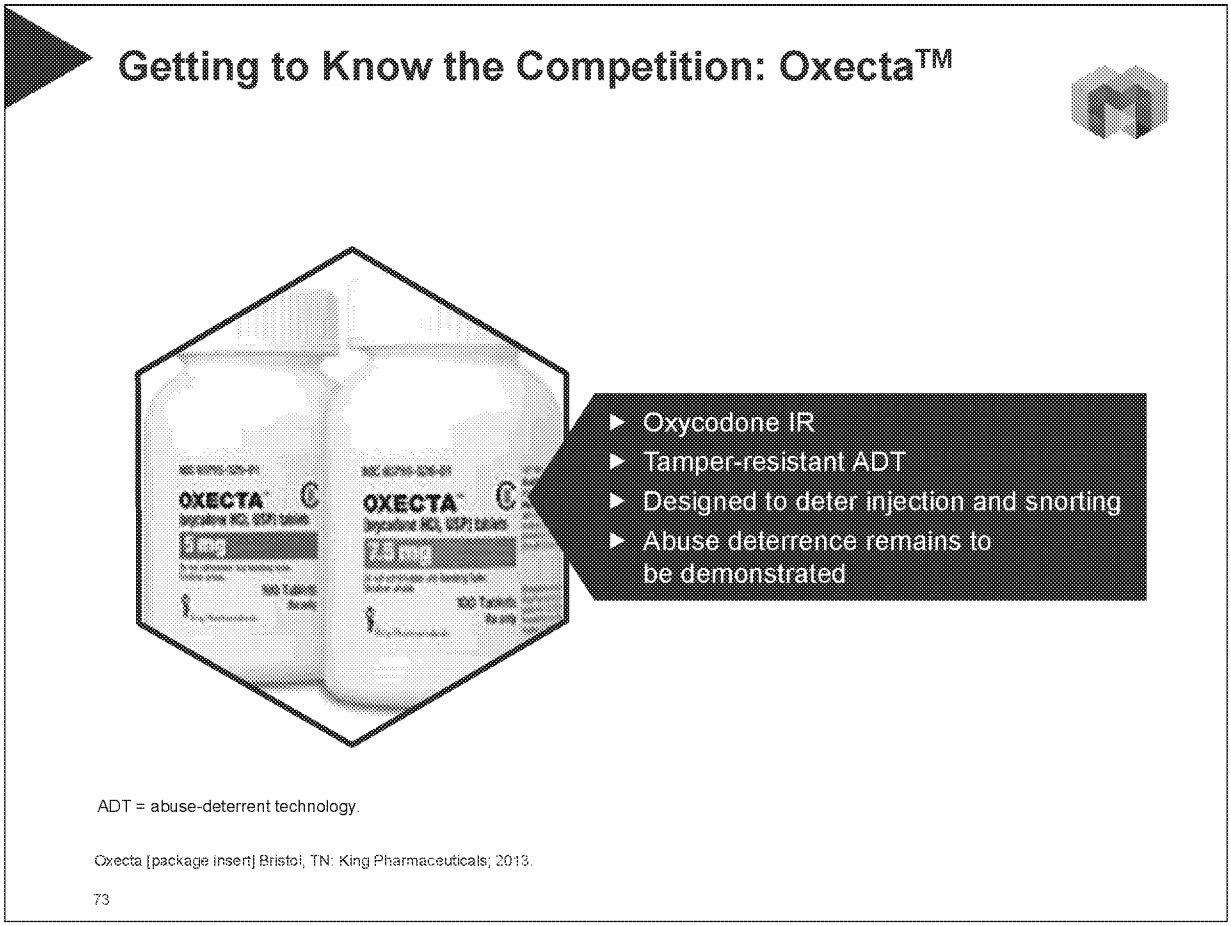


The original approval date of OxectaTM (oxycodone hydrochloride) was 1982. Oxecta was reformulated and FDA-approved in 2011, and now uses a tamper-resistant technology designed to discourage oxycodone abuse through either nasal or injectable routes of administration. Dissolution of the tablet in ethanol or water reduces it to a gelatinous compound, which complicates injection, and inhalation of the crushed tablet intranasally induces nasal burning and irritation due to the sodium lauryl sulfate.1,2 Whether or not the reformulation actually does prevent its abuse remains to be demonstrated.1

References

The Medical Letter Online. In Brief: Immediate-Release Oxycodone (Oxecta) for Pain. 2012; March 5, issue 1385:20.
Oxecta approval - OptumRx.com - RxNews®

COMMENTS:
Generic introduction



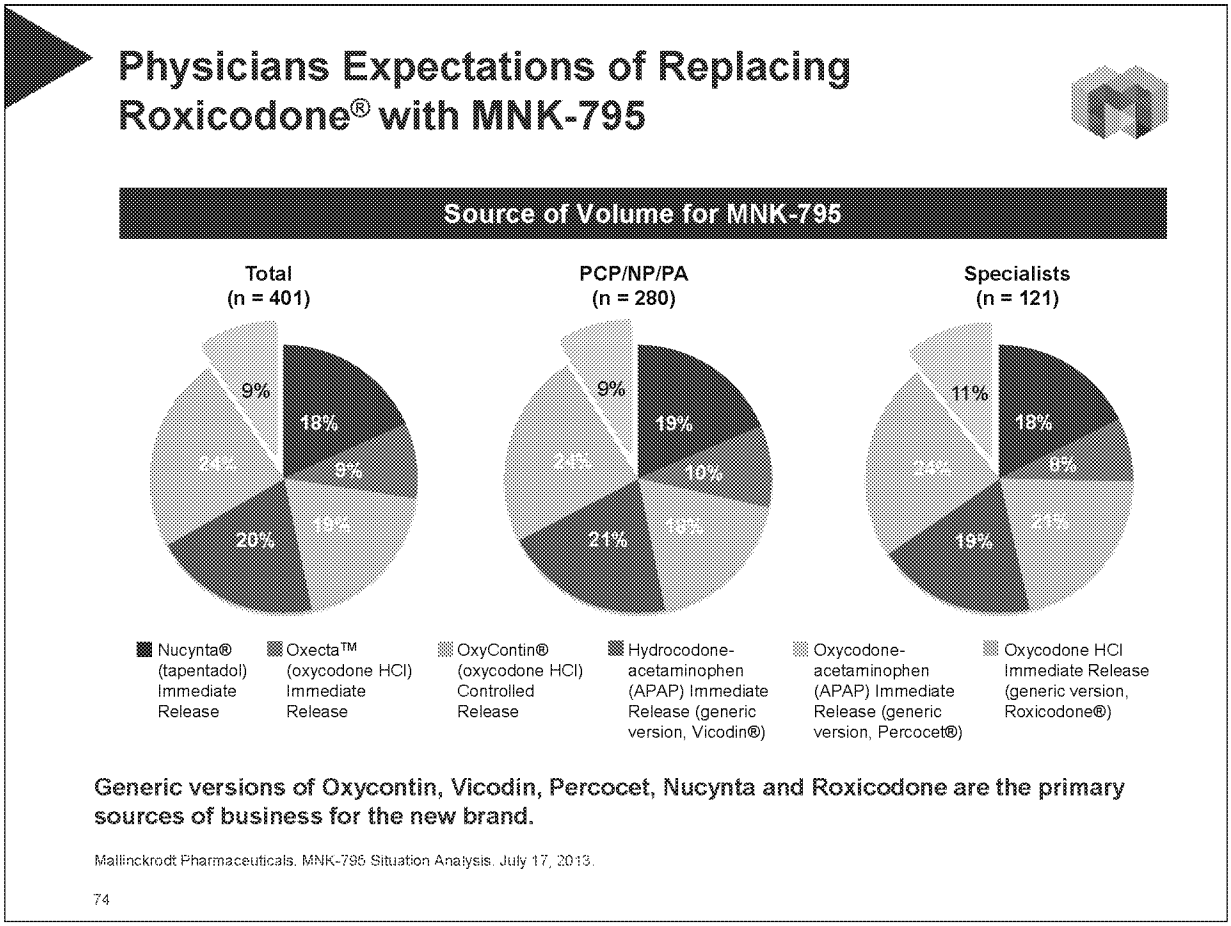
Use of similarly designed abuse-deterrent technology (ADT)-reformulated tablets has been associated with swallowing difficulties.1

OxectaTM has an indication for both acute and chronic moderate-to-severe pain. Oxecta has been found bioequivalent to other immediate-release oxycodone commercially available formulations when taken in the fasted state. When it is taken with a high-fat meal, its pharmacokinetic properties differ; however, these differences are not considered clinically significant.2

References

The Medical Letter Online. In Brief: Immediate-Release Oxycodone (Oxecta) for Pain. 2012; March 5, issue 1385:20.
Oxecta (oxycodone HCl, USP) [package insert] Bristol, TN: King Pharmaceuticals; 2013.

Example image:
http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html

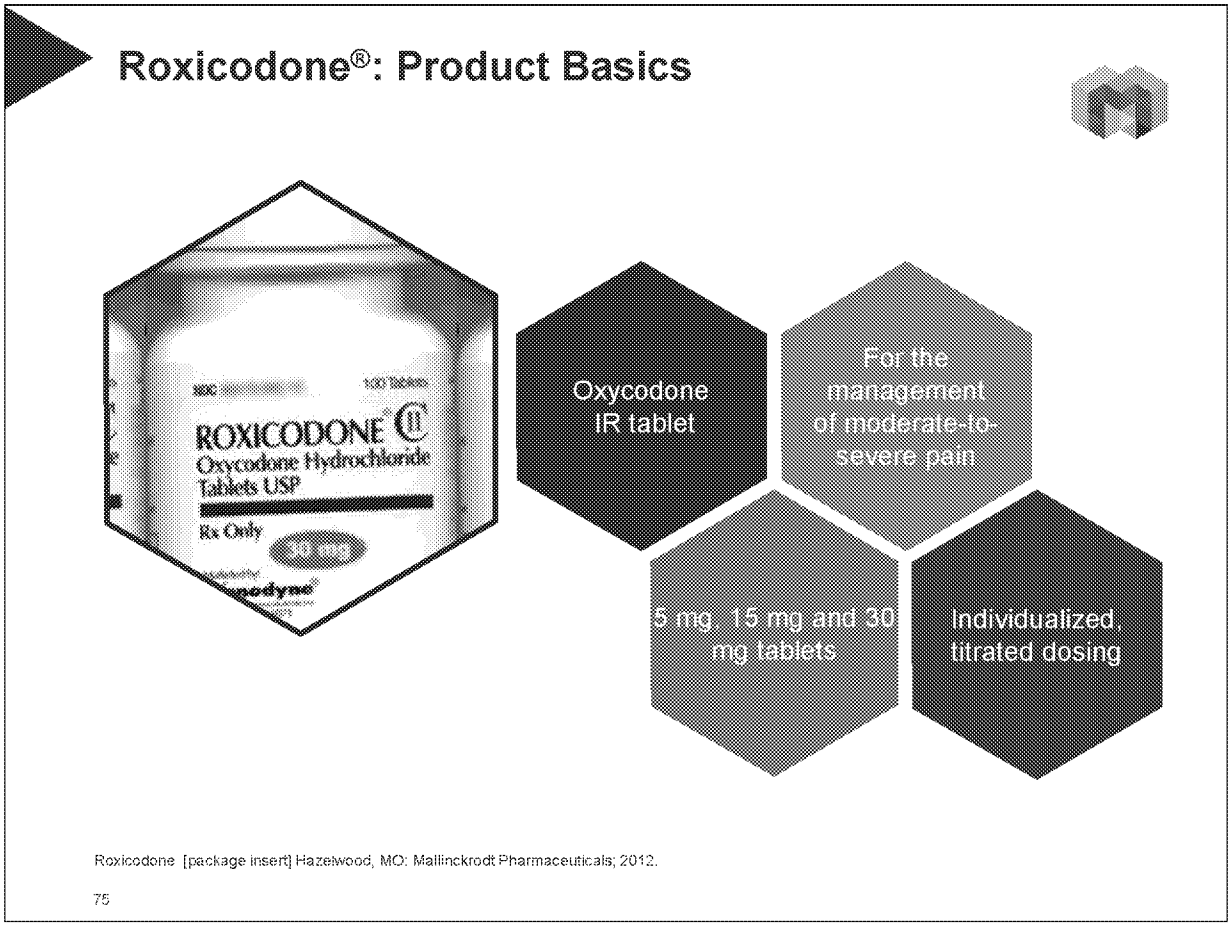


Overall, 9% of physicians would replace a portion of their oxycodone IR (generic and Roxicodone®) prescriptions with scripts for MNK-795. There was a slight difference between specialists and primary care physicians (11% vs 9%, respectively).

Reference

Mallinckrodt Pharmaceuticals. MNK-795 Situation Analysis. July 17, 2013.

Situation analysis slide 83



Roxicodone® is an immediate-release formulation of oxycodone, the same analgesic found in controlled-release OxyContin®. Individualized titration is recommended. For severe chronic pain, dosing should be carried out on a regular schedule of every 4 to 6 hours.

Reference

Roxicodone (oxycodone hydrochloride tablets USP) [package insert] Hazelwood, MO: Mallinckrodt Pharmaceuticals; 2012.

Example image:

http://trade.indiamart.com/details.mp?offer=4417098748

Roxicodone PI p 5A

Roxicodone PI p 5A

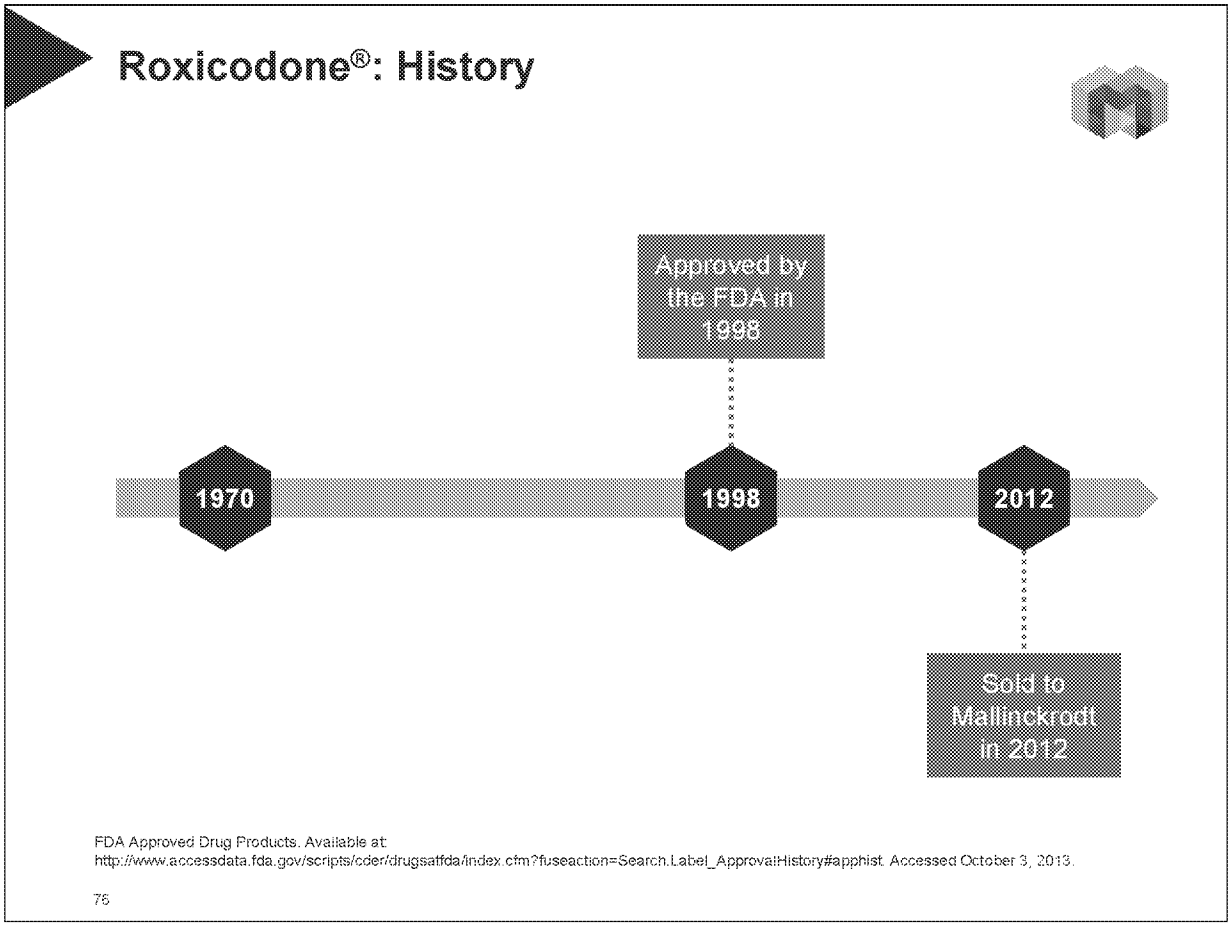
Roxicodone PI p 11A

Roxicodone PI p 12A

Roxicodone PI p 11B

Roxicodone PI p 5A

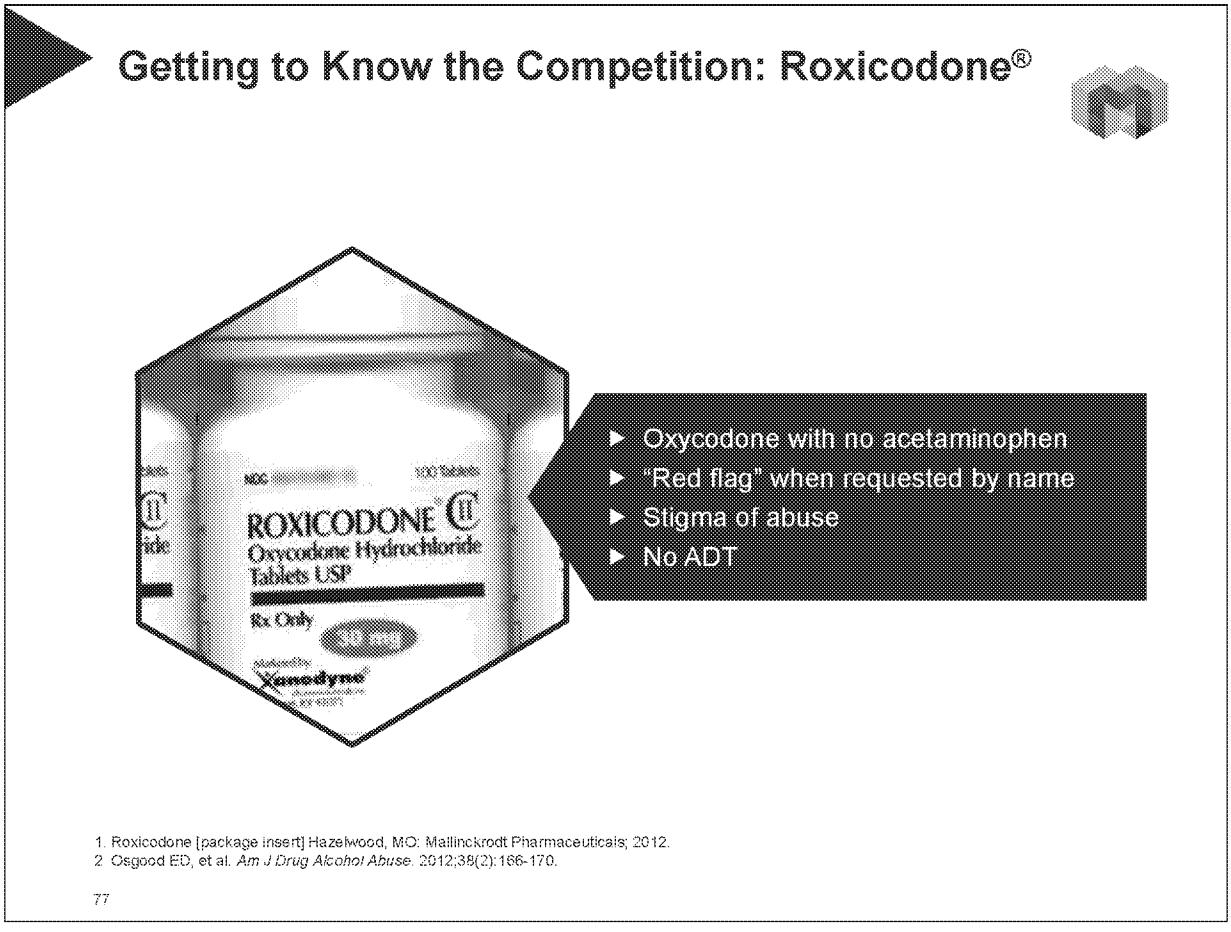
Roxicodone [package insert] Hazelwood, MO: Mallinckrodt Pharmaceuticals; 2012.



The original approval date of Roxicodone® (oxycodone hydrochloride) was October 26, 1998, FDA application number (NDA) 020932. Roxicodone was originally licensed to Roxane. A reformulation was granted to Xanodyne Pharmaceuticals in 2009, and it was then sold to Mallinckrodt in the year 2012.

Reference

FDA Approved Drug Products. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed October 3, 2013.



Roxicodine is simply oxycodone without the acetaminophen. When requested by name it raises a "red flag" in the eyes of physicians who prescribe opioids for pain and pharmacists who fill prescriptions because there is a stigma of abuse attached to the brand, which has no ADT technology.

Reference

1. Roxicodone [package insert] Hazelwood, MO: Mallinckrodt Pharmaceuticals; 2012.
2. Osgood ED, Easton TA, Trudeaus JJ, Katz NP. A brief survey to characterize oxycodone abuse patterns in adolescents enrolled in two substance abuse recovery high schools. Am J Drug Alcohol Abuse. 2012;38(2):166-170.

Example image:
http://www.123rf.com/photo_4890831_pills-spilling-out-of-a-tipped-over-pill-bottle-onto-a-dollar.html

Summary

- Targeted competitors include Oxycontin®, Vicodin®, Percocet®, Nucynta® and Roxicodone.
- Vicodin and Percocet have been on the market for nearly 40 years.
- In 2006 Americans were written 130 million prescriptions for hydrocodone-containing products.
- Hydrocodone combos capture the vast majority of the acute pain market.
- Oxecta™ and Nucynta® ER have grown substantially over the last year while Nucynta has experienced negative growth.

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